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# CONTENTS

## NUMBER 13, OCTOBER 1910

	PAGE
The Pulse immediately preceding the Epileptic Attack. By Alexander G. Gibson, T. Saxty Good, and R. Greenwood Penny. With Plate 1 . . . . .	1
Influenzal Septicaemia, with a Short Review of the Present Status of Bacillus Influenzae. By Hugh Thursfield . . . . .	7
Hereditary Haemophilia: Deficiency in the Coagulability of the Blood the only Immediate Cause of the Condition. By Thomas Addis . . . . .	14
A Further Note on Haematoporphyrinuria not due to Sulphonal. By T. K. Monro . . . . .	33
Two Cases of Acute Endocarditis. By John Cowan, A. M. Kennedy, A. R. Paterson, and John H. Teacher. With Plates 2 and 3 . . . . .	35
Tuberous (Tuberos) Sclerosis. By J. S. Fowler and W. E. Carnegie Dickson. With Plates 4-6 . . . . .	43
Coupled Rhythms of the Heart. By John Cowan and W. T. Ritchie. With Plates 7-18 . . . . .	55
The Outlook of Sufferers from Exophthalmic Goitre. By W. Hale White . . . . .	89
Association of Physicians of Great Britain and Ireland. Minutes of Proceedings of Annual General Meeting, 1910, held at Liverpool . . . . .	109

## NUMBER 14, JANUARY 1911

The Bacteriology of Human Bile with especial Reference to the Typhoid Carrier Problem. By J. F. Windsor . . . . .	118
On Carcinoma originating in the Suprarenal Medulla in Children. By R. S. Frew. With Plates 19-21 . . . . .	123
Notes upon Alternation of the Heart. By Thomas Lewis. With Plate 22 . . . . .	141
The Influence of Certain Factors upon Asphyxial Heart-block. By Thomas Lewis and B. S. Oppenheimer. With Plates 23-25 . . . . .	145
On Chylous and Pseudo-chylous Ascites. Part II. By R. L. Mackenzie Wallis and H. A. Schölberg . . . . .	153
On Pneumococcal Peritonitis. A Paper based upon a Series of Fifty-seven Cases in Children and One in an Adult. By Harold Rischbieth . . . . .	205
A Résumé of some of the Evidence concerning the Diagnostic and Clinical Value of the Wassermann Reaction. By Hugh Wansey Bayly . . . . .	232
Critical Review. Vertigo. By Sydney Scott . . . . .	242

## NUMBER 15, APRIL 1911

Infection of the Urinary Tract in Children by Coliform Organisms. By W. M. Jeffreys. With Plates 26 and 27 . . . . .	267
The Third Sound and <i>b</i> Wave in Slow Heart Action; some possible Fallacies in the Interpretation of Records. By J. Davenport Windle . . . . .	283
Paroxysmal Tachycardia of very brief Duration. By E. E. Laslett . . . . .	295

	PAGE
Modern English Cardio-vascular Teaching: a Rejoinder. By Thomas Lewis. With Plates 28 and 29 . . . . .	301
A Study of the Alterations of the Hydrochloric Acid in the Gastric Juice, due to Carcinoma of the Stomach. By George Graham . . . . .	315
The Influence of Salicylates on the Cardiac Lesions of Chorea. By E. A. Cockayne . . . . .	336
The Viscosity of the Blood: a Review. By Clifford Allbutt . . . . .	342
The Influence of Bacterial Emulsions on Phagocytosis. By F. Golla . . . . .	368
Tuberculin in the Diagnosis and Treatment of Tuberculosis. By E. C. Hort . . . . .	377
On Oxycephaly. By H. Morley Fletcher. With Plates 30-38. . . . .	385
Critical Review. The Treatment of Gastric Ulcer. By Edmund I. Spriggs . . . . .	399

## NUMBER 16, JULY 1911

Some Points in relation to the Aetiology of Auricular Fibrillation. By C. E. Lea. With Plate 39 . . . . .	423
Observations on the Relationship of the Heart-beat to <i>Pulsus alternans</i> . By J. Davenport Windle. With Plate 40 . . . . .	435
On the Analysis of Gastric Contents. By P. N. Panton and H. L. Tidy . . . . .	449
The Systolic Pressure at Different Points of the Circulation in the Child and the Adult. By Leonard Findlay . . . . .	489
A Contribution to the Study of the Function of the <i>a-v</i> Bundle. By Peter F. Holst and G. H. Monrad-Krohn. With Plates 41-46 . . . . .	498
Essential Renal Haematuria. By W. Hale White . . . . .	509
Critical Review. The Use of Tuberculin in so-called 'Tuberculous' Glands. By George E. Waugh . . . . .	521

## INDEX OF CONTRIBUTORS

ADDIS, T. Hereditary Haemophilia: Deficiency in the Coagulability of the Blood the only Immediate Cause of the Condition . . . . .	14
ALLBUTT, C. The Viscosity of the Blood: a Review. . . . .	342
BAYLY, H. W. A Résumé of some of the Evidence concerning the Diagnostic and Clinical Value of the Wassermann Reaction. . . . .	232
COCKAYNE, E. A. The Influence of Salicylates on the Cardiac Lesions of Chorea . . . . .	336
COWAN, J. Two Cases of Acute Endocarditis. With Plates 2 and 3 . . . . .	35
——— Coupled Rhythms of the Heart. With Plates 7-18 . . . . .	55
DICKSON, W. E. C. Tuberculous (Tuberos) Sclerosis. With Plates 4-6 . . . . .	43
FINDLAY, L. The Systolic Pressure at Different Points of the Circulation in the Child and the Adult . . . . .	489
FLETCHER, H. M. On Oxycephaly. With Plates 30-38 . . . . .	385
FOWLER, J. S. Tuberculous (Tuberos) Sclerosis. With Plates 4-6 . . . . .	43
FREW, R. S. On Carcinoma originating in the Suprarenal Medulla in Children. With Plates 19-21 . . . . .	123
GIBSON, A. G. The Pulse immediately preceding the Epileptic Attack. With Plate 1 . . . . .	1



	PAGE
GOLLA, F. The Influence of Bacterial Emulsions on Phagocytosis . . . . .	368
GOOD, T. S. The Pulse immediately preceding the Epileptic Attack. With Plate 1 . . . . .	1
GRAHAM, G. A Study of the Alterations of the Hydrochloric Acid in the Gastric Juice, due to Carcinoma of the Stomach . . . . .	315
HOLST, P. F. A Contribution to the Study of the Function of the <i>a-v</i> Bundle. With Plates 41-46 . . . . .	498
HORT, E. C. Tuberculin in the Diagnosis and Treatment of Tuberculosis . . . . .	377
JEFFREYS, W. M. Infection of the Urinary Tract in Children by Coliform Organisms. With Plates 26 and 27 . . . . .	267
KENNEDY, A. M. Two Cases of Acute Endocarditis. With Plates 2 and 3 . . . . .	35
LASLETT, E. E. Paroxysmal Tachycardia of very brief Duration . . . . .	295
LEA, C. E. Some Points in relation to the Aetiology of Auricular Fibrillation. With Plate 39 . . . . .	423
LEWIS, T. Notes upon Alternation of the Heart. With Plate 22 . . . . .	141
——— The Influence of Certain Factors upon Asphyxial Heart-block. With Plates 23-25 . . . . .	145
——— Modern English Cardio-vascular Teaching: a Rejoinder. With Plates 28 and 29 . . . . .	301
MONRAD-KROHN, G. H. A Contribution to the Study of the Function of the <i>a-v</i> Bundle. With Plates 41-46 . . . . .	498
MONRO, T. K. A Further Note on Haematoporphyrinuria not due to Sulphonal . . . . .	33
OPPENHEIMER, B. S. The Influence of Certain Factors upon Asphyxial Heart-block. With Plates 23-25 . . . . .	145
PANTON, P. N. On the Analysis of Gastric Contents . . . . .	449
PATERSON, A. R. Two Cases of Acute Endocarditis. With Plates 2 and 3 . . . . .	35
PENNY, R. G. The Pulse immediately preceding the Epileptic Attack. With Plate 1 . . . . .	1
RISCHBIETH, H. On Pneumococcal Peritonitis. A Paper based upon a Series of Fifty-seven Cases in Children and One in an Adult . . . . .	205
RITCHIE, W. T. Coupled Rhythms of the Heart. With Plates 7-18 . . . . .	55
SCHÖLBERG, H. A. On Chylous and Pseudo-chylous Ascites. Part II . . . . .	153
SCOTT, S. Critical Review. Vertigo . . . . .	242
SPRIGGS, E. I. Critical Review. The Treatment of Gastric Ulcer . . . . .	399
TEACHER, J. H. Two Cases of Acute Endocarditis. With Plates 2 and 3 . . . . .	35
THURSFIELD, H. Influenzal Septicaemia, with a Short Review of the Present Status of <i>Bacillus Influenzae</i> . . . . .	7
TIDY, H. L. On the Analysis of Gastric Contents . . . . .	449
WALLIS, R. L. M. On Chylous and Pseudo-chylous Ascites. Part II . . . . .	153
WAUGH, G. E. Critical Review. The Use of Tuberculin in so-called 'Tuberculous' Glands . . . . .	521
WHITE, W. H. The Outlook of Sufferers from Exophthalmic Goitre . . . . .	89
——— Essential Renal Haematuria . . . . .	509
WINDSOR, J. F. The Bacteriology of Human Bile with especial Reference to the Typhoid Carrier Problem . . . . .	113
WINDLE, J. D. The Third Sound and <i>b</i> Wave in Slow Heart Action; some possible Fallacies in the Interpretation of Records . . . . .	283
——— Observations on the Relationship of the Heart-beat to <i>Pulsus alternans</i> . With Plate 40 . . . . .	435

# THE PULSE IMMEDIATELY PRECEDING THE EPILEPTIC ATTACK

By ALEXANDER G. GIBSON, T. SAXTY GOOD, AND  
R. GREENWOOD PENNY

With Plate 1

IN the course of a research whose object was to determine in what way, if any, the action of the circulatory organs in epileptics differs from that in normal persons, it has been our good fortune to obtain satisfactory tracings immediately preceding and up to the fit in five epileptic major attacks. Many other such attacks have been observed without the aid of accurate instruments by noting the colour of the face and by feeling the pulse, but the impression that such observations leaves on our minds is that they are inaccurate and that little attention should be paid to them. The circumstances attending an epileptic attack, even though it be expected by the observer, are such that the ordinary palpation of the pulse cannot be interpreted aright; the tendons near the radial artery often become tense and raise the palpating fingers from the surface of the artery, and it is even possible that an occasional clonic spasm in the forearm muscles communicated to the flexor tendons may simulate a pulse-beat. Such errors, at least in the period preceding the convulsion, are either absent or greatly lessened by mechanical methods of recording, especially if the pulsations be taken not at the wrist but from the armlet of a sphygmomanometer applied to the upper arm. In the observations here recorded the tracings were taken with an Erlanger's sphygmomanometer, using an external pressure that was usually below the minimum blood-pressure. The experiments consisted in taking long tracings at varying external pressures, together with a record of the respiration. The patient during the time lay comfortably on a bed; the arm might become a little cyanosed but the circulation still continued, and no complaint of discomfort was on any occasion made by the patient. We are of the opinion that the constriction thus produced never either excited or accelerated the onset of a fit, for the same patient on other occasions with the same procedure had no fit, and many other cases we have examined in this way for periods of an hour or less on several occasions have never had a fit. The patient in every case, when he knows the conditions of the experiment, loses interest in it altogether and falls into a drowsy state; it is in this state that we have observed the fits to appear. Although it has not been possible to observe the earlier stages

of epilepsy or mild cases, our patients being drawn from the Asylum class, we have paid more attention to the 'idiopathic' forms in those who are still mentally efficient enough to take some part in the Asylum work.

### *Abbreviated Clinical Notes.*

*Case I.* W. P. T., male, aged 26. The patient comes of a very fair stock and there is no relative insane. In the previous history there is no disease of importance. The fits began at 7 years of age with no ascertainable antecedent; they were very frequent at first, sometimes being as many as fourteen in the day. At the present time he has a series of fits, usually about five, every three weeks, the first of which begins between 6 and 7 a.m. Each fit has well-marked tonic and clonic stages, and it is often three-quarters of an hour before he regains consciousness. His mental condition is one of mild dementia; he helps willingly in the wards, is somewhat emotional, and of the usual religious temperament. His education is fair, having gained the fourth standard at school. At the period of his fits he is confused and mildly suspicious. In body he is tall, well-built, and, except for a dull expression, he has not the epileptic facies; his complexion is smooth and healthy. There is no sign of bodily disease in any organ.

*Case II.* A. S., male, aged 22, previously a farm labourer. There is no insanity in the family, but none of his kinsfolk are even moderately endowed mentally. His father, though able to support a family in poor circumstances, is mentally ill-developed for his class. There is no history of previous disease. The fits began at 13, and the first occurred during a thunderstorm when he was out in the fields with a team of horses. He is said at that time to have been struck by lightning. After an occasional fit he was free for a period of two years, but they returned and have gradually been getting more frequent. He has about twenty fits per month and frequent petit mal attacks. The major fits last about a minute and consist of tonic and clonic stages. After some of the slighter ones he is able to get up and walk about in five to ten minutes. His mental state is one of dementia. His education is imperfect and he is said to have reached the fifth standard at school. He is a good worker and easy to manage except at his 'fitty'<sup>1</sup> times, when he is morose. He is a well-built man of medium height with an epileptic facies. There is no gross bodily disease, but there is some tremor of his upper lip in talking.

### *Description of Observations.*

All the tracings were taken on the slowly moving drum of an Erlanger sphygmomanometer, a speed which is so arranged that each pulsation of the brachial artery shows as a separate upstroke. Unfortunately no time-marker was fixed to the instrument when these records were taken. In all the figures the upper tracing represents the respiration taken by placing a rubber ball, in connexion with a tambour, underneath a loose abdominal belt; in this tracing each upstroke represents an inspiration and each fall a return to the

<sup>1</sup> This term, which is sufficiently expressive not to need further comment, is used habitually by the attendants at Littlemore Asylum; we are not aware of its use elsewhere or its equivalent in other asylums.

position of thoracic rest. It will be noticed that in all the records the respirations are markedly irregular; sometimes an occasional sighing respiration is seen (Fig. 1), now and again a suspicion of Cheyne-Stokes respiration (Figs. 1 and 2), or, as in Fig. 5, slow tonic waves superimposed upon the general respiratory undulations. In our opinion these variations bear no intimate relation to the fit, though they may be an expression of the conditions in the epileptic brain. They are seen in many epileptics quite apart from the fits or the 'fitty' state, they vary much in the same patient from day to day, and they are often to be found in patients without epilepsy, especially in neurasthenia. The lower tracing, which like the upper is to be read from left to right, is the pulsation in the brachial artery transmitted through the inflated bag to the tambour.

In the first fit observed (Plate 1, Fig. 1, Case I) the external pressure in the armlet was 78 mm., and the absence of any further note of the pressure in the course of the tracing means that no alterations in the level of the mercury column were noticed; such alterations being due to leakage of air from the apparatus or from circulatory alterations in the patient's arm. It will be seen that towards the middle of the tracing is a deep respiration followed by a short pause, and that in the latter half the type is somewhat of a Cheyne-Stokes character. The blood-pressure record is even except for the slight depression that occurs with the deep respiration. Immediately preceding the irregular movements of the lever which indicate the stage of tonic spasm the upper and lower limits of the pulse oscillate somewhat, but there is no more than a slight lessening of the amplitude of pulsation, and even in the imperfect record of the pulsations when the tonic spasm has begun there are indications that cardiac action is uninterrupted.

Plate 1, Fig. 2 (Case II) shows considerable irregularity in the respiratory tracing. The blood-pressure tracing, though taken at the external pressure of 100 mm., has a small amplitude; it shows well the respiratory undulation of pressure that some persons show more than others. In the second half of the tracing the amplitude lessens much and again increases towards the place where the irregularities which mark the onset of the fit begin. Here again there is the same oscillation in the general level of the tracing that was seen in Fig. 1; but again there is no stoppage or marked alteration of the heart's action suggested.

Plate 1, Fig. 3 (Case II) was taken with an external pressure of 90 mm., the minimum being the same. The respirations are irregular but the blood-pressure record is for the most part even; there is, however, a pause just beyond the middle of the tracing where a beat has apparently failed. Immediately after there is a period with a quicker heart-beat, which becomes normal again and finally quickens immediately before the fit. Pulse-beats continue right up to the tonic spasms with regularity and only a trivial alteration in general level.

Plate 1, Fig. 4 (Case II) was taken at an external pressure of 80 mm. (minimum blood-pressure 100 mm.). The early part shows nothing of interest not previously demonstrated in the preceding tracings. The interest of the later part lies in this, that the onset of the fit was gradual and allowed of a more detailed

study. Three points are marked on the tracing; these were made during the time the record was being taken. At *a* detectable tonic movements of the head began, at *b* they increased, and at *c* a tetanic spasm of the whole body set in. The fit undoubtedly began at *a*; the patient at the time was probably unconscious, and yet subsequently for a number of beats the pulsations are quite regular; immediately before *b* the irregularities noticed in the previous tracings occur and there is no significant or marked alteration of cardiac action.

Plate 1, Fig. 5 (Case II), taken with an external pressure of 70 mm. (minimum blood-pressure 90 mm.), is of interest because the observer was feeling the pulse throughout the period. At the point marked *x* the pulse disappeared at the

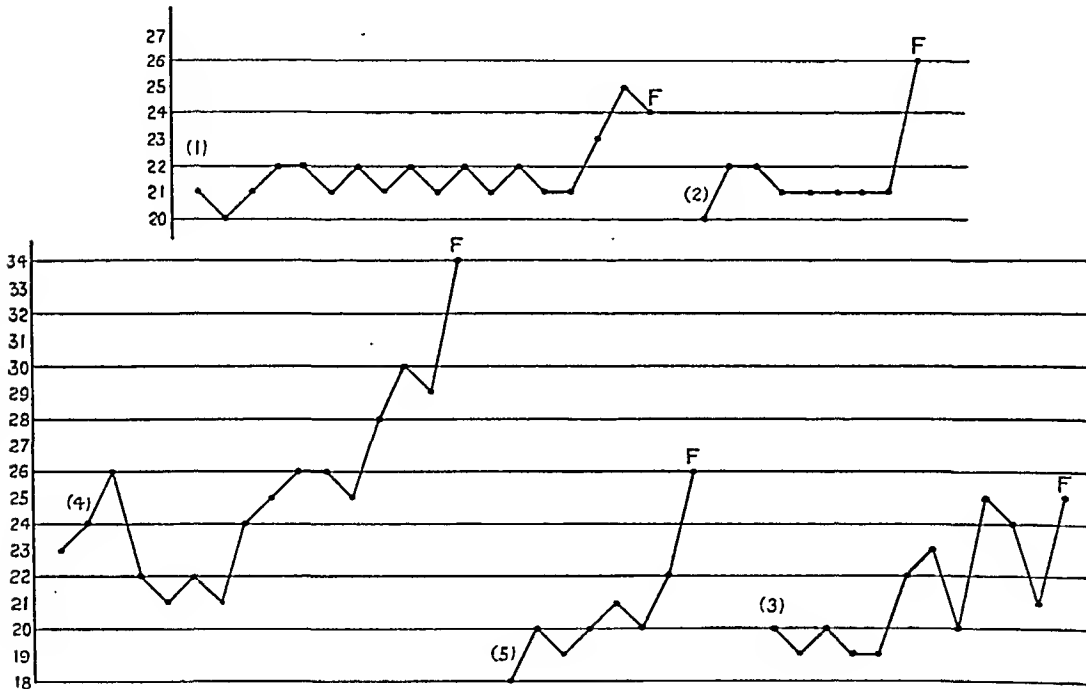


FIG. 6. Graphic record of the rate of the heart-beat throughout each tracing; the abscissae represent successive time intervals of one centimetre of the tracing, the ordinates indicate the number of heart-beats in each centimetre. The rate of the heart is seen gradually to increase towards the onset of the fit (F).

wrist and only occasional beats could be felt subsequently until the fit began. It will be seen, however, that this is only apparent, for pulsation little less in amplitude was evident in the armlet tracing. We are not certain of the explanation of this observation; the slight diminution in the pulsation will not admit of any marked alteration of blood-pressure, and such alteration as is suggested is an increase, not a decrease, in general blood-pressure (see later).

A quickening of the pulse rate preceding the fit is recorded by Munson, and is evident in the tracings that he publishes; it is evident also in our tracings. In order to demonstrate the presence or absence in each tracing we have counted the number of pulse-beats centimetre by centimetre of each tracing

and have plotted them on squared paper. We were unfortunate in not having a time-marker, but the drum used rotated evenly and smoothly and we believe there is no error from this source. The results are shown in Fig. 6, where the ordinates represent the number of pulse-beats per centimetre of tracing; in each record there is a general tendency for the pulse rate to rise towards the onset of the fit, and the highest rate in three instances is actually at the onset of the fit; in fact in the fourth record, that with the delayed onset, tonic contractions were actually in being for the last two centimetres of the tracing in which it is possible to count the beats: this tracing has the highest pulse rate of any.

We might assume with some reason that since the pulse is quickened the blood-pressure would tend to be raised; in the tracing from Erlanger's instrument we have some indications of the changes in blood-pressure when such occur. If the external pressure in the armlet be raised by stages of 10 mm. from zero to above the maximum, then the amplitude of the pulsations will increase until the external pressure is equal to the minimum pressure in the artery, that is, the pressure between the pulse waves. From this point, as the external pressure is raised, the amplitude will diminish gradually. The point that concerns the problem before us is this:—the external pressure being the same as the minimum internal pressure, if the general blood-pressure rises or falls the amplitude of the tracing will diminish; the external pressure being less than the minimum internal pressure, if the blood-pressure rises the amplitude will diminish, if it falls the amplitude will increase. It may also be said that an increase in the mean blood-pressure in the arteries whose pulsations are communicated to the armlet, will cause a general rise in the level of the tracing, and that a decrease in the same will cause a fall in the level of the tracing. Too little is known to indicate all the factors at work, so that a full explanation of the variations in the tracings could not profitably be attempted, but we would direct attention to Figs. 1 and 5. In Fig. 1 the external pressure (78 mm.) is below the minimum blood-pressure (80 mm.) previously ascertained; at the end of the tracing just before the fit the amplitude is markedly lessened and there is a definite rise in the level at two places; both these suggest a rise in blood-pressure. In Fig. 5, with an external pressure of 70 mm. and a minimum blood-pressure of 90 mm., the end of the tracing gets definitely less in amplitude and the general level rises, which again points to the same conclusion.

### *Discussion and Conclusions.*

We venture to publish these few records because we feel that until objective methods are consistently used, the explanation of the mechanism of the fit in epilepsy will remain in the region of conjecture. A. E. Russell, in an exceedingly able paper published in the Transactions of the Royal Society of Medicine and more recently in the Goulstonian Lectures, supports the old view that the fit in epilepsy is caused by a sudden lack of arterial blood in the brain,

from certain observations of his own puts forward the proposition that in some cases at least there is a cessation of the pulse before the fit. In an earlier paper he admits that certain observers, notably Gowers, have recorded the fact that the pulse persists throughout the fit. The only graphic records of which we are aware are those of Munson previously referred to, who found a slight quickening immediately preceding the fit in all the records he obtained. The records put forward in this paper prove that there is no alteration of the pulse sufficiently definite to affect the amplitude of the wave up to the point when clonic convulsions prevent its being properly recorded, and in more than one record the fit had been noticed to be in progress before the record was interfered with. As regards the blood-pressure, we are able to assert that in none of the records does such a lowering of general blood-pressure take place as to suggest that cerebral anaemia from a general cause could have produced the convulsion, for in conditions in which lowered blood-pressure produces a general spasm, as for instance in Stokes-Adams disease, the convulsions occur after a time interval of several seconds after the pulse has stopped. In more than one of our tracings the patient was noticed to be in the fit and unconscious while little recognizable change was evident in the pulse or blood-pressure. We do not wish, however, to exclude the stoppage of the pulse as a possible cause of epilepsy; moreover we are strongly impressed with the views put forth in Russell's paper; but so far as these records go, and the type of epilepsy that our two cases represent, we must look, for the mechanism of the fit, rather to a local cause in the brain, such as a vaso-motor spasm, than to a general cause such as lowering of blood-pressure from cardiac inhibition or splanchnic dilatation.

#### REFERENCES

- Munson, J. F., *Journ. Amer. Med. Assoc.*, Chicago, 1908, l. 681.  
 Russell, A. E., *Lancet*, Lond., 1906, ii. 152; *Trans. Royal Soc. Med.*, Med. Sect., Lond., 190; *Lancet*, Lond., 1909 (i), 963, 1032, 1094.

#### DESCRIPTION OF FIGURES

FIG. 1. Case I, minimum blood-pressure 80 mm., armlet pressure 78 mm. The upper tracing is the respiration, the lower the Erlanger record. The occurrence of the fit is marked at the end of the tracing.

FIG. 2. Case II, minimum blood-pressure not ascertained at the time of taking the tracing, armlet pressure 100 mm. Upper tracing, respiration; lower, Erlanger record.

FIG. 3. Case II, minimum blood-pressure 85-90 mm., armlet pressure 90 mm.

FIG. 4. Case II, minimum blood-pressure 100 mm., armlet pressure 80 mm. Upper tracing, respiration; lower, Erlanger record. Towards the end of the tracing, at *a*, the patient showed definite movements indicating the commencement of the fit, at *b* they became more general, and at *c* the whole body became convulsed.

FIG. 5. Case II, minimum blood-pressure 90 mm., armlet pressure 70 mm. Upper tracing, respiration; lower, Erlanger record. The pulse at the wrist was being felt throughout and at *x*, towards the end of the tracing, it disappeared for a few seconds.



Fig 1

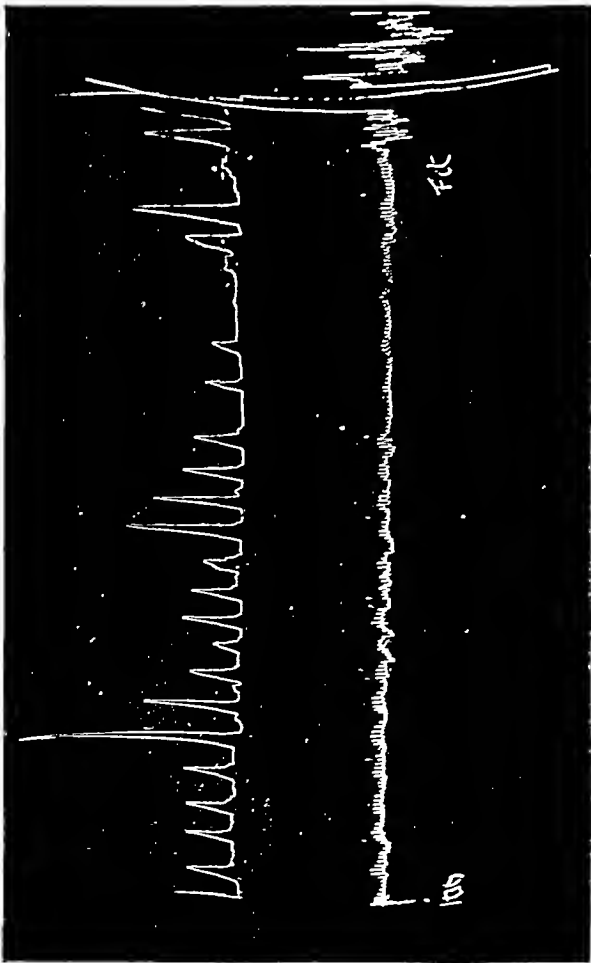


Fig 2



Fig 5

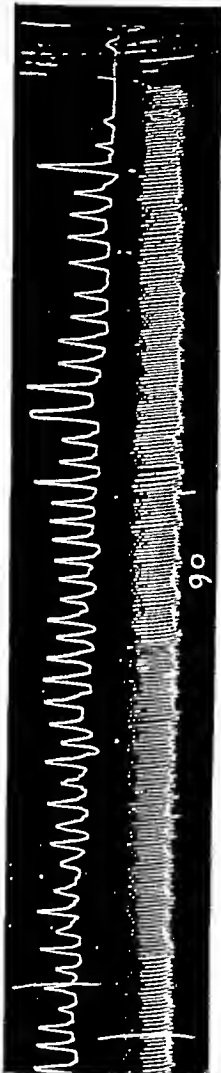


Fig 3



Fig 4





# INFLUENZAL SEPTICAEMIA, WITH A SHORT REVIEW OF THE PRESENT STATUS OF BACILLUS INFLUENZAE

By HUGH THURSFIELD

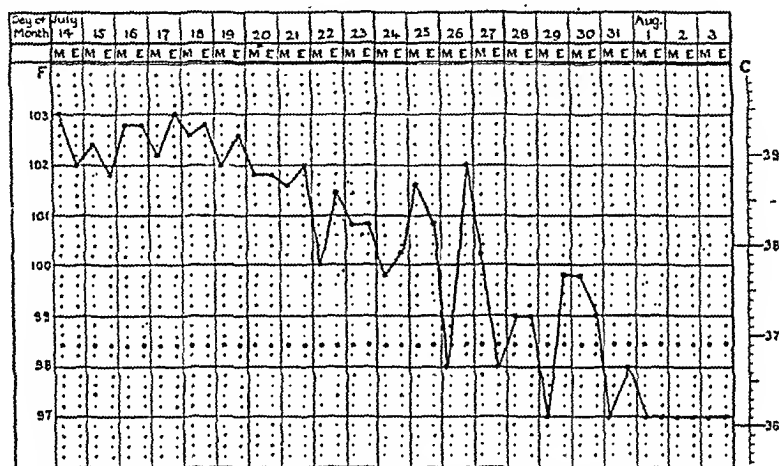
DURING the great epidemic of influenza in 1889-91, Pfeiffer described a bacillus which has been widely accepted as the cause of the disease. His original description of the organism as a slender bacillus, often exhibiting a tendency towards polar staining, negative to Gram's stain, and growing only on haemoglobin-containing media, still holds good, and though different strains of the organism occasionally exhibit in culture features which were not included in Pfeiffer's original description, especially a tendency to grow out into long filamentous forms, yet these features have been so frequently observed in undoubted strains of the *B. influenzae* that they are universally accepted as characteristic of the organism. Pfeiffer and his school laid down the proposition that where organisms of the *B. influenzae* type are found there is an influenzal infection, and called certain similar organisms which were found in non-influenzal affections pseudo-influenza bacilli, attempting a differentiation on grounds of morphology only. Joehmann, who has studied the subject, is of the opinion that no essential morphological difference exists between the organisms derived from influenzal and non-influenzal sources.

So far then there is a general agreement among bacteriologists as to the morphological characters of the organism which Pfeiffer discovered, but there is a wide divergence of opinion as to its occurrence in the blood; Pfeiffer and his followers declaring that the *B. influenzae* is rarely found in the blood of patients, while Canon and others have found it in a large percentage of cases. Joehmann in summing up this question inclines to Pfeiffer's opinion, and believes that when the organism appears in the blood it is usually a post-mortem or agonal phenomenon.

The two cases which I record here are therefore of great interest in regard to this disputed point, and when considered in the light of recent work on so-called influenzal meningitis, lead, I think, inevitably to the conclusion that what we have been content hitherto to regard as a specific organism is, in reality, only one of a group, the members of which have similar, if not identical, morphological and cultural characteristics, but different pathogenic properties.

*Case I.* J. L., a City policeman, aged 22, who had never had a day's illness in his life, and declared that until this attack he had not known what a headache was, was admitted to Dr. West's Ward at St. Bartholomew's Hospital on July 14, 1909, with high fever and severe headache. Two weeks previously

he had gone off duty with a severe chill and sore throat, but had returned to duty on July 7 for one day. An attack of severe frontal headache incapacitated him again on July 9, and he had been in bed since. On admission, his pulse was 92 per min., full and regular; his temperature 102.4, and his respirations 24 per min.; his tongue was thickly coated; he was sweating profusely, and besides the headache had severe pain in the back. Examination revealed nothing in the condition of the heart, lungs, or abdominal organs, which would account for the condition. His reflexes were natural; his sensation unimpaired; he had no paralysis; his eyes were normal, both as regards movements, reflexes, and the appearances of the fundus. An enumeration of his leucocytes gave 9,600 per cm.; a Widal's agglutination test with *B. typhosus* was negative; and a lumbar puncture yielded 3 c.c. of a clear fluid, which contained no organisms, and showed no increase of cellular elements. A blood cultivation (5 c.c., from



the median basilic vein) made on July 19 gave a growth in one tube of an organism resembling in every particular the *B. influenzae* of Pfeiffer. A second cultivation on July 23 was sterile.

On July 20 and the following days, his head was held stiffly and somewhat retracted; the headache was of extreme severity, causing him to scream with the pain. His condition remained practically the same until July 24, when he felt much more comfortable. On July 26 the headache recurred and persisted till July 29. On July 31 his temperature fell to normal, and thenceforward convalescence was uninterrupted.

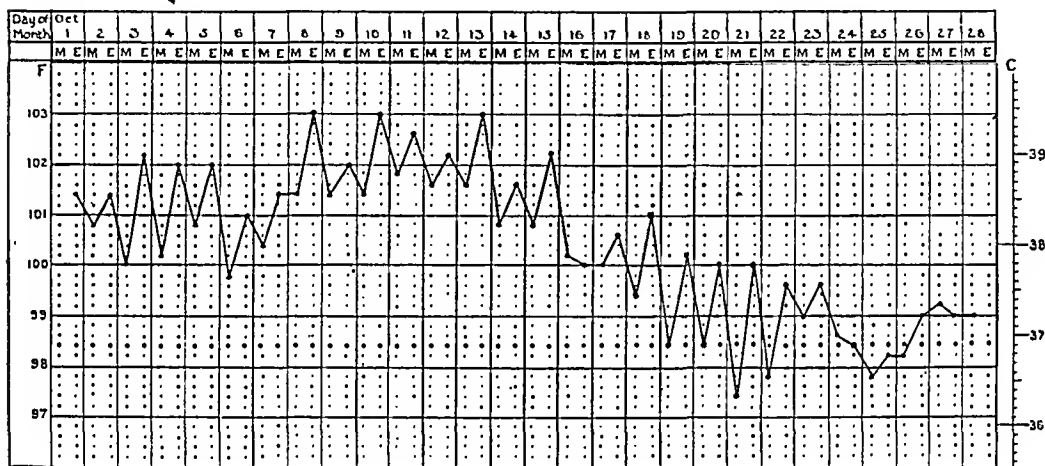
Throughout his illness his pulse was rarely above 100 per min., and his respirations were never laboured. His urine, which was scanty in quantity for the first three days, never contained any albumin. The prominent feature of his illness was the severity of the headache, which at one period gave rise to the suspicion that he had an intracranial tumour or abscess.

*Case II.* A. M., a groom, aged 35, was admitted to Mr. Bowlby's Ward at St. Bartholomew's Hospital with pain and swelling in the right leg. The pain and swelling had begun in the right foot three weeks previously, and had spread slowly up the calf of the leg. On admission the right leg was swollen from ankle to knee; the skin shining and tense, pitted easily on pressure, and was very tender. No venous cord could be felt. His temperature was 101.6° and pulse 128 per min.

Three days later, October 4, a thickened cord could be felt running up the back of the right leg to the popliteal space. On October 7 his general condition became suddenly worse, and a patch of pneumonic consolidation was discovered

in the lower lobe of the left lung. It was noted at the same time that the area of praecordial dullness was increased, and the following day pericardial friction was heard and felt over the heart. Two days later the left leg became swollen, tender, and oedematous, and a thickened cord similar to that in the right leg was found. On October 12 a blood culture revealed the presence in the circulation of a bacillus, which morphologically and culturally resembled the *B. influenzae* of Pfeiffer. At this time the patient's general condition was extremely serious, but on October 15 he began to show signs of improvement, and gradually returned to complete health.

This patient was most seriously ill during the period of the pneumonia and pericardial inflammation, and was believed to be suffering from an acute septicaemia; the leucocyte count at the grave period of his illness was 11,000 per c.mm.



The organisms found in these two cases corresponded perfectly to the bacillus of Pfeiffer. They grew only on haemoglobin-containing media, occurring in small transparent colonies on the surface of blood-agar slopes. The organisms were slender, short bacilli, non-motile, Gram-negative, with an occasional long filamentous element. In the first case the organism isolated was not inoculated into an animal, but that isolated from the second case was injected into a mouse subcutaneously; the animal suffered no ill effects.

From the clinical aspect the first patient may be considered to have suffered from an attack of influenza, in the course of which there occurred an incursion of the bacilli into the blood, an event which, according to Pfeiffer, Jochmann, and other authorities, is of extreme rarity. In the second patient there was no evidence of anything resembling an attack of influenza, the affection of the veins of the right foot and leg being the earliest symptoms of illness. The occupation of this patient suggested inquiry as to the condition of the horses under his charge, and in reply to questioning he recollected that about a fortnight previous to his illness one of his horses had suffered from a nasal and ocular catarrh, and had been ill for several days. In neither case was vaccine therapy employed. Vaccine was prepared in the second case, but was not required, as improvement had begun before it was available.

Putting aside for the moment the question of bacillaemia in epidemic influenza, the number of cases in which a bacillus resembling the *B. influenzae* has been found during life is scanty. Horder has reported four cases of chronic infective endocarditis in which he was able to demonstrate such a bacillus in the blood taken from an arm-vein during life. All his cases terminated in death. Spät found bacilli of this type in a case of endocarditis and pyonephrosis during life. Slawyk, in a similar case of pyaemia with purulent arthritis of the right wrist and ankle-joints, found a bacillus which he identified as the *B. influenzae* of Pfeiffer, and Saathoff has demonstrated it in a case of broncho-pneumonia and vegetative endocarditis in a young adult. In cases of so-called influenzal meningitis the organism has been demonstrated many times in the cerebro-spinal fluid, and a few times in the blood during life.

Returning now to epidemic influenza, Pfeiffer, Weichselbaum, and others maintain that the bacillus rarely, if ever, gets into the blood-stream; while Canon and, of recent authors, Ghedini maintain that it is easily demonstrated in a large percentage of cases. Jochmann, from his own work and a review of the literature, is inclined to side with Pfeiffer, and believes that the presence of the bacilli in the blood is rare except as an agonal phenomenon. The balance of evidence is certainly in favour of this conclusion, but the work of Cohen on influenzal meningitis, to which I shall recur, suggests the possibility that the two opposing schools were working with different organisms, and that under the designation of *B. influenzae* of Pfeiffer there are at least two, and possibly several, distinct species at present confounded with one another.

With this possibility in view, it becomes of importance to know the various conditions in which a bacillus of the type in question is found, and what are the lesions which may be fairly attributed to it. So far we have seen that an organism of this type is generally accepted as the cause of epidemic influenza, and that in this disease it rarely occurs in the blood during life; but that in a limited number of cases of endocarditis a similar organism has been isolated from the blood during life in pure culture; and that in the two cases recorded here a similar organism has been the cause of an illness of a septicaemic type.

The next question that arises is the occurrence of the organism in cases of disease due to other infections, and the rôle it plays in them. It has been found with a fair degree of frequency in the broncho-pneumonic patches of children dead of diphtheria, usually in conjunction with streptococci and pneumococci. In similar circumstances it has been demonstrated in measles, in scarlet fever, and in the lungs of patients dead of tuberculosis. In these cases there does not appear to be any reason for supposing that the influenza bacilli exerted any influence upon the course of the illness, and it is probable, according to Jochmann in his careful review of the subject, that they were present as saprophytes.

In the case of whooping-cough, however, the question is more complicated. There is a general agreement among all the more recent workers at this subject that a bacillus of the *B. influenzae* type is present in the tough masses of mucus expectorated during the early stages of the cough in practically pure culture.

Organisms of this type have been isolated by various observers (Jochmann and Krause, Elmassian, Jchle and others), but none have succeeded in differentiating their microbes from Pfeiffer's bacillus. Bordet, on the other hand, has isolated a Gram-negative haemophilic bacillus which he has been able to grow after a time on ordinary laboratory media without the addition of blood. Bordet's own description of this organism is that in size and shape it resembles the *B. influenzae*: 'examined *in situ* it is usually rather longer and plumper, but during the process of subcultivation it becomes smaller and smaller, till finally it appears as a mere point even under the highest powers.' He adds that when trained to grow on agar media without the addition of blood it grows in a thick white streak like a staphylococcus. Bordet's organism at present holds the field as the probable cause of whooping-cough. Experiments made with it in respect of agglutinative power, of fixing the complement, and lastly of its curative power in the form of a vaccine, while not conclusive, all lend support to its claims.

From the consideration of the occurrence of *B. influenzae* in the specific infectious diseases, I turn to the records of its appearance in other conditions, and notably in affections of the meninges. It is agreed that although meningeal symptoms are not uncommon in epidemic influenza, the occurrence of a definite purulent meningitis is a rare event. Recently, however, attention has been called to a form of purulent cerebro-spinal meningitis, in which the only organisms found are slender rods resembling both in morphological and cultural characteristics the *B. influenzae*. It would seem probable that such cases have been overlooked in the past, since of recent years an increasing number has been recorded. In 1907 Adams was able to collect twenty-one cases of the affection from the literature, and Cohoe has, in 1909, added three others; all of these were proved either by culture of the organism from the cerebro-spinal fluid during life, or from the pus after death. Up till last year the identity of the organism found in these cases of meningitis with the *B. influenzae*, though often suspected, had never been definitely challenged, but in April, 1909, Cohen published an important paper in which he maintains the thesis that this form of meningitis is in reality a new disease, due to an organism which while morphologically and culturally identical with Pfeiffer's bacillus, can be differentiated from it by its pathogenic effects upon rabbits and guinea-pigs. In three cases he has isolated this organism, and shown that it occurs not only in the meninges, but also in the blood, in the broncho-pneumonic lesions of the lungs; in the effusions into the pleural and pericardial sacs, and in the purulent fluid of joints. Parenthetically, I would refer here to the case reported by Dudgeon and Adams in 1907, where an organism which they considered to be the *B. influenzae* was found in the pus of inflamed joints, in the lungs, and in the cerebro-spinal fluid, and pus from the meninges. It would seem possible that these authors were dealing with Cohen's bacillus, but animal inoculation was not practised.

Cohen's organism was injected intravenously into rabbits and caused death

in 12 to 20 hours. After exalting its virulence thus by passage, it was inoculated subcutaneously into another rabbit, and caused death on the thirteenth day. The microbe was recovered in pure culture from the heart's blood, the fluids of the pleura, pericardium, and peritoneum, and from the meninges. These experiments have been repeated with identical results. Cohen has further succeeded in immunizing rabbits against this organism to such a degree that eighty times the normal lethal dose has no effect upon them; and, further, the serum of such rabbits has a highly protective action when inoculated into a non-immunized animal twenty-four hours before the lethal dose of the organism is given. He has also shown that animals immunized with the *B. influenzae* are not protected against this organism, and that their serum has no protective power. Agglutination experiments were unsatisfactory; the two organisms could not be differentiated.

He notes a morphological feature, which in two cases of so-called influenzal meningitis I have been able to confirm: namely, that in subculture the organism 'prend un aspect bizarre, tourmenté (formes gigantesques en poire, en massue, grands filaments contournés en S prenant mal la couleur et présentant par places de grosses granulations chromatiques)'. My own inoculation experiments with organisms obtained from the blood and meningeal pus were entirely unsuccessful.

Organisms identical with the *B. influenzae* have been obtained in cultivations made from the pus of cases of otitis media, and in four cases recently at St. Bartholomew's Hospital in pus from the antrum of Highmore. In three of these cases I obtained pure cultures without any difficulty; no other organism appearing in the culture tubes, although a few Gram-positive cocci were seen in the smears. The organisms thus obtained, even when subcultivated for long periods, never presented the bizarre involution forms to which Cohen refers in the quotation given above and which I have seen in the meningeal cases. They were also quite innocuous to guinea-pigs.

### *Conclusions.*

(1) There is a general consensus of opinion that the organism originally described by Pfeiffer as the *B. influenzae* is the cause of epidemic influenza.

(2) That in epidemic influenza it is rarely found in the blood, except as an agonal phenomenon.

(3) That nevertheless, in certain cases of endocarditis and of septicaemia, an organism identical in all respects with *B. influenzae* can be isolated, and is in all probability the cause of the illness.

(4) That organisms identical in all respects with the *B. influenzae* are found in a number of patients who die of the acute specific fevers, especially in the broncho-pneumonic areas.

(5) That Bordet's bacillus, an organism identical in shape and size with the *B. influenzae*, but capable of differentiation in culture, is the probable cause of pertussis.

(6) That a bacillus identical with *B. influenzae*, both in morphological and cultural characteristics, but capable of differentiation by a study of its pathogenic effects upon animals, is the cause of a septicaemic form of cerebro-spinal meningitis.

(7) That an organism identical in all respects, morphological, cultural, and pathogenic, with *B. influenzae* is a cause of suppuration in the middle ear and the sinuses of the nose.

(8) That a consideration of the foregoing propositions renders it certain that we must in future recognize that the organisms hitherto described as *B. influenzae* are not all identical with it, but, like the streptococci, staphylococci, and the colityphoid family, belong to a group the various members of which possess very different pathogenic powers.

#### BIBLIOGRAPHY.

- Bordet, *Brit. Med. Journ.*, 1909, ii. 1062.  
Cohen, *Ann. de l'Inst. Pasteur*, Paris, 1909, xxiii. 273.  
Cohoe, *Amer. Journ. of Med. Sci.*, Phila., 1909, cxxxvii. 74.  
Dudgeon and Adams, *Lancet*, Lond., 1907, ii. 684.  
Ghedini, quoted from Jochmann.  
Horder, *Trans. Path. Soc.*, Lond., 1906, lvii. 58 ; 1907, lviii. 265 ; *Practitioner*, Lond., 1908, lxxx. 714.  
Jochmann, Lubarsch u. Ostertag. *Ergebnisse der allgem. Pathol.*, Wiesbaden, 1909, xiii, Abteil. i. 107.  
Pfeiffer, *Zeitschr. f. Hyg. u. Infektionskrankh.*, Leipz., 1893, xiii. 357.  
Saathoff, *Münch. Med. Woch.*, 1907, liv. 2, 2220.  
Slawy, *Zeitschr. f. Hyg. u. Infektionskrankh.*, Leipz., 1899, xxxii. 443.  
Spält, *Berlin. Klin. Woch.*, 1907, xlv. 1207.



## HEREDITARY HAEMOPHILIA:

### DEFICIENCY IN THE COAGULABILITY OF THE BLOOD THE ONLY IMMEDIATE CAUSE OF THE CONDITION<sup>1</sup>

By THOMAS ADDIS

IN 1896 Wright first definitely established the fact of the delayed coagulation of the blood in this disease. Since then it has been confirmed by Sahli, Morawitz and Lossen, Weil, Baum, Kottmann and Lidsky, Nolf and Herry, and others. No one using modern methods has found a normal coagulation time in haemophilic patients. But the constancy of this pathological feature does not exclude the possibility that there are other causes at work in producing the symptoms of the disease. There are certain difficulties in the way of accepting it as the sole cause. Indeed, when some of the clinical phenomena are considered, it would seem that a deficient coagulability of the blood is inadequate in itself to explain all the facts. If the blood in haemophilia were incoagulable then indeed it would not be necessary to look further. But it is not. On the contrary, very large clots form in the wounds of these patients, though blood may continue to ooze from them for hours or days. If then the diminution in coagulability is not of such a degree as to prevent coagulation in the wound, how can it be regarded as the direct cause of the continuance of the haemorrhage? Again, how does it account for the fact that the wound cavity may soon be filled with clot which completely arrests the bleeding, and that nevertheless hours later haemorrhage may recur and continue indefinitely? Surely during the period when the bleeding had ceased, the blood in the wound must have had ample opportunity for complete coagulation? These difficulties might be explained by assuming that there was a deficient formation of fibrin, so that the clot was loose and easily dislodged; but this appears to be negatived by the results of Sahli's experiments. He showed that, *ex vitro at least*, the fibrin formed in the delayed coagulation of haemophilic blood was as great in amount as that produced in the more rapid clotting of normal blood, and that it is impossible to distinguish one clot from the other, both are equally firm and dense.

Wright, though holding fast to the deficient coagulability as the proximate cause, recognizes that it does not explain all the facts. Sahli, who attempts a complete theory of the condition, is obliged to assume a hypothetical chemical defect in the tissues of the vessel walls, which consists of an absence in them of the substance, thrombokinase, which normally initiates the process of coagu-

<sup>1</sup> The work in connexion with this paper has been done under the conditions of tenure of a Carnegie Research Scholarship.

lation. In this way he explains the continuance of haemorrhage in spite of clotting in the wound, for no clot forms in the ruptured vessels themselves, although it may occur when the blood leaves them and comes into contact with the extravascular tissues of the wound. This assumption, however, is purely speculative and unsupported by any experimental data. Morawitz and Lossen found that the addition of thrombokinase to haemophilic blood causes a very rapid coagulation. From this fact they conclude that the delay in coagulation is due to a deficiency of thrombokinase in the tissues in general. In a subsequent paper I shall bring forward results from which it may be concluded that they are mistaken in this view, but assuming it to be correct, the above objections still remain to the defective coagulation thus explained being the sole cause of the phenomena seen in the haemorrhages in haemophilic subjects. Sahli's theory is certainly the most complete, and yet Dahlgren in a paper published last year, in which he describes the death from loss of blood of three haemophiles, is unable to accept it. He asks how, if it is true, the recurrence of bleeding after its complete cessation is to be explained, and why the amount of bleeding should be so variable, sometimes continuing for a long time from a slight cut, at other times ceasing more quickly from a much more extensive wound. The general opinion of most of those who have had an opportunity of watching the onset and development of haemorrhages in haemophilia is that there must be some other factor at work, such for instance as an abnormal fragility of the capillaries, whose mode of action must be made clear before a complete explanation of all the phenomena of the disease can be said to have been attained.

All are agreed, however, that the defect in coagulation is the only constant pathological sign of the disease. The object of the present paper is to bring forward evidence that it is not necessary to go beyond this fact in the search for the proximate cause of haemophilia. It will be shown that there is a direct relation between the severity of the symptoms and the degree of retardation of coagulation; that after the lapse of some time the blood flowing from a wound in a haemophilic still shows the characteristic delay in clotting, and that this is well marked even in recurrent haemorrhage from wounds in which coagulation has taken place. Finally, the peculiarity of the clot which forms in haemophilic wounds is described, and it is shown how bleeding may continue in spite of it, or may cease only to recur. This abnormality in the nature of the coagulation arises as the direct result of the great prolongation of the time required for coagulation to complete itself. This therefore, it is maintained, is the sole proximate cause of haemophilia, sufficient in itself to explain all the symptoms.

### *I. The coagulation time of the blood.*

Twelve cases were examined. They were descended from six different haemophilic stocks in Scotland, England, and Germany. In none of these families was there any known instance of a departure from the characteristic

type of transmission, i.e. through the females to the males. Full clinical accounts of several of these cases have been or will be published. A short sketch of their histories will be found at the end of this paper.

The coagulation time of the blood of people in health is constant. The actual time required depends on the temperature and the method by which it is estimated. The method mainly used was a modification of McGowan's method (1), and the temperature was 20° C. Under these circumstances normal blood coagulates in 10 minutes. Variations between 9 and 11 minutes occur and are due to experimental error. These figures are based on observations (1) in which every coagulation time represented an average of three consecutive estimations, but in the following times found in haemophilic patients each figure is a single observation and not an average.

### Case I.

Date.	Coagulation time in minutes and seconds.	Date.	Coagulation time in minutes and seconds.	Date.	Coagulation time in minutes and seconds.
Sept. 18	9. 0 12.30 10.45	Sept. 23	17.45 19.15 12.45	Sept. 25	15.15 13.45 13.45
Sept. 20	16.15 16.45 21.45	Sept. 24	9.30 9.45 11.30	Sept. 27	15.45 16.30 17.30
Sept. 21	12.15 11.15 15.15	(5 hours later)		Oct. 11	18.30 16.30 18.30
Sept. 22	13. 0 15. 0 15. 0		15.45 14.15 15.45	Oct. 18	21. 0 20. 0

*Case II.* Three estimations were made. Times of 16 min. 15 sec., 13 min. 45 sec., and 15 min. 45 sec. were obtained.

### Case III.

Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.
Aug. 21	62 59	Aug. 25	80 52	Sept. 8	55 55
Aug. 22	53 58 50	Aug. 26	74 61	Sept. 10	55 57
Aug. 23	50 50 51	Aug. 30	86 87	Sept. 11	84 54
Aug. 24	49 63 70	Aug. 31	91	Sept. 18	71
		Sept. 4	71 62	Sept. 19	60 77
		Sept. 5	75 87	Sept. 23	75

### Case IV.

Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.
Sept. 19	53 59 63	Sept. 22	90 78 84 96	Sept. 23	44 96

*Case V.*

Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.	Date.	Coagulation time in minutes.
Sept. 15	40	Sept. 16	56	Sept. 20	79
	36	Sept. 18	59		80
	38		49	Sept. 23	43
					60

*Case VI.* The coagulation times were 72 min. and 73 min. Five days later a time of 87 min. was found.

*Case VII.* In this case two estimations gave times of 71 min. and 55 min.

*Case VIII.* The times were 70 min., 74 min., and 72 min.

*Case IX.* The times were 79 min., 92 min., 85 min., and 83 min.

*Case X.* The times were 71 min., 63 min., 61 min., 75 min., 68 min., and 64 min.

*Case XI.* The coagulation time with my method was as a rule between 30 and 40 minutes.

In this case the method of Morawitz and Bierich was also used. A hollow needle sterilized by heating in liquid paraffin was inserted into the median basilic vein, and about 2.5 c.c. of blood was run into each of a series of test-tubes, which were then kept at a constant temperature until they could be inverted without spilling. The coagulation time was the period elapsing between this point and the time at which the blood was drawn. When the temperature was 30° C. times of 43 min., 45 min., 47 min., 48 min., 47 min., 47 min., 44 min., 46 min., 44 min., 42 min., and 42 min. were obtained. An experiment carried out under the same conditions on normal blood gave times of 18 min., 20 min., 20 min., 18 min., 17 min., 17 min., 17 min., and 17 min.

A week later the coagulation time was again taken with this method, but the temperature was 37° C. The results were 46 min., 52 min., 52 min., 45 min., 51 min., and 53 min. With normal blood the times were 13 min., 12 min. 45 sec., 14 min. 30 sec., 12 min. 15 sec., 14 min., and 13 min. 45 sec.

*Case XII.*

Feb. 24. 70 min., 65 min., 75 min., 80 min., and 72 min.

Feb. 28. 86 min., 60 min., 45 min., 87 min., 86 min., and 65 min.

March 2. 75 min., 80 min., 85 min., 63 min., and 89 min.

March 4. 53 min., 59 min., 58 min., 70 min., 75 min., and 57 min.

These results show conclusively, therefore, that there is a delay in the coagulation of haemophilic blood, a delay which in some cases is very pronounced and which far exceeds any retardation of coagulation observed in other diseases (2).

But although the fact that there is a great delay in coagulation is quite clearly and definitely shown, the actual figures are obviously only very approximately correct, for there are often wide variations even in the results of consecutive observations. The experimental error must certainly be a very large one. Nevertheless there can be no doubt as to the substantial reliability of the method, when a number of determinations are made and the average is taken as representing the coagulation time. In Case XII the coagulation times were taken by this method, and also with the method of Morawitz

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and Bierich, at a time when wide variations in coagulability were taking place as the result of therapeutic injections, and the results agreed well with each other. Smaller variations, such as perhaps occur under physiological conditions in these patients, are, however, obscured by the experimental error. The clinical histories of some cases of haemophilia suggest a certain periodicity in the appearance of the symptoms, and it is quite possible that these depend on variations in the coagulability of the blood. To determine whether there are in reality changes in the time, Dr. Finlay and I have commenced independent observations on the same days with the two methods in Case XII. So far our results agree closely and show some degree of variation, but the point cannot be said as yet to be settled.

## II. *The relation between the severity of the symptoms and the coagulation time of the blood.*

Clinically the cases fall naturally into three groups. The first is that in which the patients were scarcely ever free, for any length of time, from some sign or other of the disease, even in the absence of any traumatic accident greater than those inseparable from ordinary life. Cases III, IV, V, VI, VII, VIII, IX, X, and XII are included in this group. None of them, during the period when they were under observation, was suffering from any severe or disabling haemorrhage, but in all of them very slight degrees of trauma were sufficient to induce bleeding. For example, Case III knocked his hand against an iron rail, and although the force with which he did so was not sufficient to lead to any appreciable pain, effusion took place into the metacarpophalangeal joint. He twisted his knee slightly coming downstairs, and it became swollen with blood. On another occasion an effusion into the knee occurred, although he could not remember having hurt it at all. In Case IV also the slightest injury to his knees gave rise to pain and swelling, and the signs of fluid in the joint. In him and in Case V small puncture wounds in the fingers were followed by the development of haematomas. Case VI brushed his arm against the door when leaving a room, and next day a bruise had appeared. Case XII was confined to bed, but even here there was bruising which was evidently the result of his raising himself from the bed on his elbows. In all these cases it was the exception not to find a bruise on some part or other of the body, or an effusion into one or more joints.

The second group is that in which trivial accidents did not lead to observable haemorrhage. Case XI is the only one who comes in this group. He was often free from all symptoms for weeks on end. The maximum of trauma which led to bruising in him was considerably greater than that necessary to produce it in the cases of the first group. For instance in Case VI the application of a moderately tight bandage on the arm was followed by bruising, yet in Case XI, though bandages quite as firm were often applied, there was never the least trace of bruising. Again, on one occasion in drawing off blood from a vein

in the arm in Case VI, the needle, instead of going directly through the skin into the vein, ran into the subcutaneous tissues. A small haematoma appeared and there was deep staining of the skin from the wrist to the axilla. A similar accident occurred once or twice with Case XI, but there was never any haematoma and the amount of bruising was very slight.

In the third group a still greater degree of injury was required to lead to any appreciable amount of haemorrhage. The only practical difference between the patients in this group and ordinary individuals was that on the occurrence of such a wound or injury as would always produce an appreciable amount of bleeding in any one, the bleeding in them persisted for a longer time. Cases I and II are in this group. In both of them there had been no sign for years that they were in any way different from other people. This, however, was only due to the fact that for a long time they had not sustained any severe injury. For when Case I had a tooth extracted the bleeding persisted for 10 days, and showed that his long freedom from symptoms was only a matter of degree, and was not an indication that he was completely normal.

As regards the severity of the disease, therefore, the cases are clearly separable into the three groups of severe, moderate, and slight cases. If the deficiency in coagulability is in itself sufficient to explain the symptoms, it would follow that the severer the manifestations of the disease the longer the coagulation time would be, and vice versa. That such in fact is the case will be seen in the following table, in which each case is grouped according to the degree of incidence of the clinical symptoms, and the average coagulation time of all the observations taken on the case is given :—

Severe symptoms.	Moderate symptoms.	Slight symptoms.
Case III = 68 min.	Case XI = 36 min.	Case I = 15 min.
„ IV = 74 „		„ II = 15 min. 15 sec.
„ V = 54 „		
„ VI = 77 „		
„ VII = 63 „		
„ VIII = 72 „		
„ IX = 85 „		
„ X = 67 „		
„ XII = 70 „		

### III. *A consideration of the process of coagulation in normal and haemophilic wounds.*

The coagulation times which have been given are a measure of the time required for the clotting of the first drop of blood issuing from a small puncture wound, but they do not give any indication of the changes in coagulability which take place in blood flowing from a wound, from the moment when it is inflicted up to the time when such an amount of clot has formed that the bleeding ceases. Under normal circumstances there is a rapid and progressive increase in the coagulability of each successive specimen of blood; the first drop takes the longest time and the last coagulates practically instantaneously. But



before comparing this with the results obtained by similar observations on blood from haemophilic wounds, it will be of advantage briefly to consider the present position as regards the physiology of coagulation and the explanation which is advanced of this progressive acceleration of the rate of coagulation.

There have been in the past many theories of the coagulation of mammalian blood which are now discredited or greatly modified, but certain facts remain, though the interpretation of their meaning and significance has changed. These essential facts can be put very shortly. Coagulation is the formation of fibrin. There are four factors necessary—fibrinogen, prothrombin, thrombokinase, and calcium. By the interaction of the last three thrombin is produced, and thrombin acting on fibrinogen precipitates fibrin. Fibrinogen is a globulin in solution in the plasma. The action of thrombin upon it is generally believed to consist in a cleavage of the molecule into two parts—serum-globulin, which is soluble, and fibrin, which is insoluble. Prothrombin<sup>2</sup> is a substance of unknown chemical constitution, present in circulating blood. In itself it has no action on fibrinogen, but in the presence of thrombokinase and calcium, after a certain interval of time, a change is found to have taken place in its physical and chemical properties and the new body, thrombin, is formed, whose action on fibrinogen has been noted. Thrombokinase<sup>3</sup> is also of unknown chemical constitution. It is not found in the plasma of the circulating blood, but is present in the tissues, particularly those rich in nucleo-proteins, and in the formed elements of the blood. Without it no thrombin can be formed. The greater the quantity of thrombokinase added to the blood from the tissues or formed elements, the more rapid is the change of prothrombin into thrombin. Calcium salts are also essential for the formation of thrombin. Thrombin, the result of the action of thrombokinase and calcium on prothrombin, is often called fibrin ferment, but this is an unfortunate term, since it does not possess all the properties of a ferment. Thus it acts quantitatively, that is to say, a measured quantity will coagulate a certain definite amount of fibrinogen and no more. In the act of coagulating the fibrinogen it becomes attached to the fibrin, and most of it is precipitated with it. That part which remains free after all the fibrinogen has been coagulated disappears after a short time. This is generally ascribed to the action of a substance in the plasma which is termed anti-thrombin. Although thrombokinase and calcium are necessary for the building up of thrombin, they are not required for its action once it has been formed. All fibrinogen-containing fluids, whether they contain thrombokinase and calcium or not, are coagulated when thrombin is added to them. Time is required for the formation of thrombin, but the action of thrombin once formed is practically instantaneous.

Work on coagulation has centred round the theory which Schmidt advanced towards the end of last century, after a lifetime of work devoted to this subject.

<sup>2</sup> Prothrombin was the term originally used by Alexander Schmidt, but it has been called thrombogen by Morawitz and plasmozyn by Fuld.

<sup>3</sup> Corresponds to the zymoplastic substance of Schmidt, the cytoplasm of Fuld, the tissue-coagulin of Loeb, and the thrombozym of Nolf.

Although further research has shown him to be mistaken in many details, yet the general outline of his theory remains and is now only more firmly established. Morawitz and Fuld, as the result of much painstaking work, were able to clear away many errors and misconceptions, but their elaboration of Schmidt's theory is recognized by them as not being entirely final. There remained unexplained and puzzling discrepancies in the work of different investigators, and some details in the various phenomena of coagulation were still not quite clear.

There is now, however, a theory of coagulation founded on experimental work of the most conclusive character which explains all these difficulties. Mellanby's work ends a period in the history of the gradual growth of knowledge in this department; it completely answers the old questions, and in doing so raises new problems for the future. The reason for his success lay in the fact that he was able to isolate the different factors concerned in coagulation, while the obscurity and variability of the older results were due to a want of precise knowledge as to the contents of the fluids with which these results were obtained. Solutions which were considered to contain only one of the constituents necessary for coagulation were often mixtures of two or more of these principles in varying proportions. It is indeed to be wondered at that with such confusion at the very basis of their work, they should, nevertheless, have arrived at conclusions which lie so near the truth. As an example of this confusion, Schmidt's thrombin, which has been accepted as the standard thrombin solution, is now proved to contain a varying quantity of thrombin, sometimes none at all, and its coagulative action is shown to be often due to the thrombokinase and calcium, whose presence in it were unsuspected. The meta-thrombin, on which Morawitz in his theory lays such stress, is proved to be thrombokinase. But the most important fact that Mellanby has established, and the one which more than any other makes clear the difficulties into which other observers have been led, is the relation which exists between fibrinogen and prothrombin. Fibrinogen solutions were usually assumed to contain fibrinogen only, whereas in reality prothrombin was present. In whatever way fibrinogen is obtained, prothrombin is always found associated with it,<sup>4</sup> and further, the amount of prothrombin is directly proportional to the amount of fibrinogen. The prothrombin is in a condition of absorption in the fibrinogen molecule, and the only way in which a solution of prothrombin can be obtained free from fibrinogen is by coagulating fibrinogen by the addition of a foreign thrombin. The molecule is then broken up, fibrin is precipitated, prothrombin is set free, and is found in the fluid expressed from the clot. Such a fluid has no coagulating action, except in the presence of calcium salts and thrombokinase, when it becomes a thrombin solution with very marked coagulating powers.

Mellanby's theory, very shortly expressed, is as follows: The circulating

<sup>4</sup> Prothrombin appears to be more easily destroyed than fibrinogen, and so it comes that it is possible to prepare fibrinogen solutions in which the contained prothrombin is no longer capable of activation to thrombin. Such solutions coagulate only when preformed thrombin is added to them.

blood contains fibrinogen with its absorbed prothrombin, calcium salts, and anti-thrombin. No coagulation takes place because of the absence of thrombokinase. When the tissues are wounded, the injury or destruction of the cells leads to the setting free of thrombokinase. In its presence the calcium salts unite with the prothrombin, and thrombin is formed. On account of the close molecular relation which exists between this newly formed thrombin and the fibrinogen it escapes the neutralizing action of the anti-thrombin, and fibrin is quickly formed by its action on the fibrinogen. Most of the thrombin is precipitated with the fibrin. Any fresh blood forcing its way through the clot is coagulated by thrombin, and prothrombin is thus set free, but if no thrombokinase reaches it no fresh thrombin is formed. The production of thrombin is therefore strictly limited to the sphere of the thrombokinase. That part of the thrombin which is not carried down in the fibrin is gradually neutralized by the anti-thrombin. 'The whole mechanism of coagulation is admirably adapted to produce large and rapid clotting within a wounded area, but to stop the process immediately beyond the confines of the injured tissues.'

Mellanby's theory is in the main that of Morawitz and Fuld, simplified, and at some points enlarged, and now for the first time freed from uncertainty and speculation. In the light of this theory the process of coagulation in wounds in normal and in haemophilic people may now be compared.

The following figures represent the changes in the coagulation of blood flowing from a wound in a normal person. A deep puncture was made into the thumb and the coagulation time of successive specimens of the outflowing blood was determined.

Length of time after making the wound at which the specimen of blood was taken.		Coagulation time.		Remarks.
min.	sec.	min.	sec.	
0	0	12	45	
0	30	9	30	
1	15	3	15	
2	15	1	30	
2	30	0	15?	
2	45	—	—	No more blood could be obtained

How is the rapid increase in the coagulability of each successive specimen of blood to be explained? Of the four factors in coagulation—fibrinogen, prothrombin, calcium, and thrombokinase—the first three, being already present in the blood, were necessarily constant. The only variable was the thrombokinase added to the blood from the injured tissues. The first specimen of blood spurting out instantaneously from the capillaries was in contact with the tissues for only a very short time, and, as a consequence, took up a small amount of thrombokinase. With each successive specimen not only was the flow of blood becoming progressively slower but more and more thrombokinase had time to exude from the injured tissue cells. Now the rate of the change of prothrombin into thrombin, other things being equal, depends on the quantity of thrombokinase; the more thrombokinase the more rapid the production of thrombin.

The increasing coagulability, then, was due to increasing amounts of thrombokinase. But this does not account for the instantaneous coagulation of the last specimen.<sup>5</sup> For even with large quantities of thrombokinase the formation of thrombin requires some time, it is not instantaneous. Only where preformed thrombin is added to it does blood coagulate immediately. But such preformed thrombin must have been derived from the previous coagulation of blood in the wound. Further the clotting must have been only partial, or no more blood would have flowed. This free thrombin came from the coagulation of the blood adherent to the sides of the wound. There the flow was slowest and there the concentration of thrombokinase was highest. It thus came about that the prothrombin of this part of the blood had time to change into thrombin before it was forced out of the wound. Immediately this was accomplished the newly formed thrombin coagulated the fibrinogen with which it was associated. Most of it was precipitated with the fibrin, but enough escaped partially to clot the blood in the centre of the wound, which slowly escaped from the wound, and was the last specimen obtained. But this was the end of the haemorrhage. The activation of prothrombin was proceeding, and immediately afterwards enough thrombin had been set free to completely coagulate all the blood in the wound. No more blood could then be forced out even by pressure.

The cessation of bleeding, then, was due to two forms of coagulation, which for convenience of description may be called primary and secondary. In the primary coagulation the blood was coagulated by the activation of its own inherent prothrombin. Each molecule of fibrinogen was acted on by thrombin formed from the prothrombin which was present within the molecule itself. In the secondary coagulation the blood was coagulated by preformed extraneous thrombin derived from the primary coagulation of another part of the blood. Its own prothrombin took no part in the process.

That is the course of events as they occur in a wound in a normal person. What happens when a similar wound is made in a haemophilic? A puncture wound, as far as possible of the same depth and extent, was made into the thumb of Case III and the coagulability of successive specimens of blood was estimated in the same way.

Length of time after making the wound at which the specimen of blood was taken.		Coagulation time.		Remarks.
min.	sec.	min.	sec.	
0	0	80	0	
0	15	60	0	
0	30	44	0	
0	45	32	0	Bleeding stopped <sup>6</sup>
2	45	28	0	Expressed blood
7	0	12	30	Expressed blood
12	0	—	—	No more blood could be expressed

<sup>5</sup> The coagulation time is put down as 15 sec., but this is simply the shortest time in which it was possible to determine the presence of fibrin.

<sup>6</sup> This cessation of haemorrhage was due to mechanical causes. Whenever the pressure of the outflowing blood fell sufficiently, the skin closed over the wound and prevented the exit

Here also there is the same progressive increase in coagulability. It happened that the very last drop of blood before complete coagulation set in was not obtained, but, if it had been, the instantaneous coagulation seen in the last drop from the wound in the normal person would also have been observed here. The difference is one of degree only, though it is a very marked one. For the last specimen of blood obtained, some of which had remained in the wound in contact with the tissues for nearly five minutes, did not show the immediate coagulation which was found in normal blood after two and a half minutes in spite of the fact that in that wound the blood was being constantly forced out by fresh blood. The difference is much greater than the figures themselves indicate, and reveals a great delay even under these most favourable circumstances in the formation of thrombin in haemophilic blood. It may be objected that this is not the only explanation, for thrombin might have been formed, but yet have been inefficient or unable to act because of some fault in haemophilic fibrinogen. I hope to enter fully in a subsequent paper into the cause of the delay of coagulation in haemophilic blood, and there I shall show in detail that haemophilic blood is quite as easily and readily coagulated by haemophilic thrombin as is normal blood by normal thrombin. The only possible explanation then is that the thrombin took an abnormally long time to form.

This fact alone goes some way towards explaining the length of time during which haemorrhage may continue in haemophilia, although, as will be shown, it is not in itself a sufficient reason. In this particular instance, bleeding was stopped mechanically by the closing of the skin over the mouth of the wound, and time was given for thrombin to form in the blood enclosed in the cavity of the wound. If, however, an incision had been made of such an extent as to allow the skin to retract and leave the wound open, it is easy to see that bleeding might have continued for a long time without there being any chance of the blood coagulating.

But the special characteristic of haemorrhages in haemophilia, and the point which is difficult to understand, is that in spite of the sometimes massive formation of firm clots in and around the wound, the bleeding still continues or ceases for a time only to recur. Thus in Case I, who had had a tooth extracted, the bleeding went on for ten days, and, but for treatment, would have continued for a still longer time, although large clots formed and adhered firmly to the contused gum. Fresh blood filtered up slowly and continuously through the clot and ran over into the mouth. How is the continuance of bleeding to be explained in such a case? How can it be attributed to any deficiency in the coagulability of the blood since firm coagulation has nevertheless obviously taken place?

And yet, paradoxical as it may appear, it is because of the coagulation that the bleeding continues. In such wounds in haemophiles coagulation is local instead of general. Only that part of the blood which is in immediate contact

of any more blood. On account of this plugging of the wound by the elastic recoil of the tissues it is possible with safety to introduce small hollow needles into the veins of haemophiles for the purpose of obtaining blood.

with the tissues coagulates. In doing so it forms a firm barrier against the access of more thrombokinase to the blood in the central part of the wound. Bleeding continues through a funnel of fibrin lining the sides of the wound. The reason why such a partial coagulation occurs in haemophilia will be made clearer by giving the details of an experiment on the effect on the coagulation time of haemophilic and normal blood of adding varying amounts of thrombokinase.<sup>7</sup> This was done by running various dilutions of thrombokinase through the glass tubes immediately before they were filled with freshly drawn blood. That amount of thrombokinase which remained adhering to the walls of the tube mixed with the blood and exerted its effect. The temperature was 20° C.

Thrombokinase solution.	Coagulation time of the blood of Case III. (The coagulation time without the addition of any thrombokinase was 68 minutes.)		Coagulation time of the blood of Case IV. (The coagulation time without the addition of any thrombokinase was 74 minutes.)		Coagulation time of the blood of a normal person. (The coagulation time without the addition of any thrombokinase was 10 minutes.)	
	min.	sec.	min.	sec.	min.	sec.
0.4 %	4	30	2	30	2	30
	3	0	2	30	2	0
0.1 %	5	30	5	15	3	30
	6	30	4	15	3	0
0.5 %	7	30	7	0	4	15
	8	0	7	0	4	0
0.25 %	13	30	9	0	5	45
	10	30	8	15	5	15
0.125 %	24	45	17	0	6	30
	22	30	—	—	5	15
0.062 %	36	0	33	0	6	15
	41	0	23	0	5	45
0.031 %	47	0	48	0	8	45
	45	0	75	0(?)	8	0

From these figures it is seen that while with large amounts of thrombokinase coagulation may be as rapid as that of normal blood, with smaller amounts, even such as are sufficient notably to accelerate the coagulation of normal blood, there is still a very prolonged coagulation time.

This has an evident bearing on the question of the continuation of haemorrhage in haemophilia in spite of the presence of clots in and around the wound. When an incision is made through the skin the blood streams from the vessels and fills the cavity caused by the retraction of the tissues. Thrombokinase comes from the injured cells and mixes with the blood which is in contact with the sides of the wound. It is here that there is the greatest concentration of thrombokinase and here also that the flow of blood is somewhat retarded. The coagulation of the part of the blood in contact with the tissues is thus markedly accelerated, so that it may coagulate and leave a film of fibrin adherent to the tissues. But in the more centrally situated blood the concentration of

<sup>7</sup> The thrombokinase was obtained from a human testicle. The gland was stripped of its coverings and weighed immediately after its removal from the body. It was then ground up in a mortar with sand, extracted for some hours with that amount of distilled water which gave a solution of 4 per cent. and finally filtered and heated to 100° C.

thrombokinase is not so great. Now it has been shown in the above experiment that the formation of thrombin in haemophilic blood takes a long time even in the presence of considerable amounts of thrombokinase. This part of the blood is therefore driven out of the wound before sufficient thrombin has formed to coagulate it. The pressure of the out-flowing blood is sufficient to wash away the thrombokinase from the mouths of the severed vessels and continually to drive out before it the blood in the central part of the wound, which, though it does not contain so much thrombokinase, only requires time to coagulate. The layer of fibrin on the sides of the wound increases in thickness until the point is reached at which the amount of thrombokinase which penetrates through it is no longer sufficient to induce rapid coagulation. But this is not a complete picture of what occurs, for no account is taken of the thrombin liberated in the coagulation of this peripheral blood. There is no excess of anti-thrombin in haemophilic blood,<sup>8</sup> and the question, therefore, arises why, once some thrombin has been formed, coagulation does not occur throughout all the blood in the wound. This is simply a question of degree. Rettger has shown very clearly how the coagulation of blood by thrombin is a purely quantitative process, and I have repeatedly confirmed this point. A certain minimum amount of thrombin is necessary to produce any visible coagulum at all. As the amount is increased the quantity of fibrin formed grows greater. Thrombin, therefore, does not act in this respect in the manner of a ferment, and though thrombin is produced in the wound the question whether or not it will coagulate the blood in the central part of the wound depends entirely on the quantity. If the coagulation at the periphery of the blood stream is taking place very slowly only small quantities of thrombin will be produced at any given moment, the coagulation induced will be partial, and the soft loose clot will be driven out with the stream of blood. Or, although partial, the clot may remain in the wound and stay to some extent the main force of the outflow, while still allowing some blood to trickle through its meshes. This is the usual condition in a wound of moderate severity in haemophilia. There are thus two clots in the wound: the one peripheral and due to primary coagulation by the activation of the prothrombin by means of thrombokinase; a second central and distinct from the other, not only in its position, but in the fact that it is a secondary coagulation due to extraneous thrombin liberated from the peripheral clot. Such a secondary clot has no power to induce coagulation. It contains no thrombokinase, and when all the thrombin has been neutralized, blood coming straight from the vessels and free from thrombokinase may ooze through it without being in any way affected.

I do not maintain that in every case of prolonged bleeding in haemophilia there is this absolute distinction between the primary and secondary clots. Probably a certain amount of thrombokinase will be present even in the blood in the centre of the wound, for it must be remembered that thrombokinase arises not only from the tissue cells, but that a certain amount is also derived from the

\* The grounds for this statement will be given in a subsequent paper.

formed elements of the blood when they are injured. But even though the sealing-off of thrombokinase is not absolute, the blood may take a very long time to coagulate, even if the flow of fresh blood from the vessels has been stopped by the secondary coagulum. With minimal amounts of thrombokinase the coagulation of haemophilic blood may take many hours to complete itself. If, during this period, the secondary coagulum is dislodged from the mouths of the vessels, by, for instance, a sudden rise of blood pressure, the bleeding will recur, and—since the access of large amounts of thrombokinase from the tissues is prevented by the peripheral primary layer of clot—may continue indefinitely.

This explanation of the reason for the continuance of bleeding in haemophilia in spite of the occurrence of coagulation in the wound was suggested by observations made on a haematoma which developed in Case IV. Some puncture wounds rather deeper than usual had been made into the extensor surface of the right thumb, in order to collect some blood from which to obtain serum. Bleeding ceased almost immediately, but three-quarters of an hour later, while he was washing his hands in hot water, quite brisk haemorrhage started from one of these wounds. It was apparent then that the stopping of the bleeding soon after the wound had been made had not been due to coagulation. It must rather be attributed to the elasticity of the skin, which by its recoil led to the close apposition of the lips of the wound and so to a mechanical prevention of further loss of blood. For when the skin was relaxed by hot water the wound opened and bleeding began again. Some cotton-wool steeped in freshly shed normal blood was applied and pressure exerted by a bandage. No blood soaked through, but when, three hours later, it was taken off, bleeding began again. Two estimations of the coagulability of the blood streaming from the puncture gave times of 48 min. and 49 min. Pressure again stopped the bleeding until an hour and a half later, when he took a hot bath. Shortly afterwards he came to me because blood was coming through the bandage. Blood was flowing freely, and whenever the lips of the wound were separated, a jet of blood spurted out, indicating that a small arteriole had been cut. The coagulation times of three specimens of blood from the wound were 43 min., 61 min., and 51 min.

Now it was inconceivable that after all these hours there had not been ample time for the blood remaining in the wound to completely coagulate if it was in contact with the tissues and thus taking up large quantities of thrombokinase from them. In Case III, as has been shown, complete coagulation in the wound took place in twelve minutes. The only explanation appeared to be that in this case complete coagulation had only occurred locally. Only the film of blood in direct contact with the tissues, in which therefore the concentration of thrombokinase was high, had clotted. The amount of thrombin set free from this primary coagulation had not been sufficient to completely coagulate the blood in the centre. A small pool of partially coagulated blood was left there in communication with the cut vessel and cut off from the tissues, and therefore from the access of thrombokinase by the peripheral primary clot. When the wound opened, this central blood was washed out and the flow



continued until pressure closed the lips of the wound again. It must be remembered that the coagulation times given of blood flowing from the wound do not represent the actual time which each particular specimen of blood would have taken to coagulate if it had remained in the wound. For the contact of blood with glass, as I have shown elsewhere (3), has a great effect in accelerating coagulation on account of the injurious action it exerts on the formed elements, which leads to the setting free of thrombokinase from them. In the wound itself there was no such foreign body, and if the shutting off of thrombokinase was absolute, and all the thrombin from the primary clot had been neutralized, the blood in the centre of the wound would have remained fluid indefinitely.

The subsequent course of events appeared to confirm the correctness of this view. Pressure maintained for two days prevented any further bleeding, and when the bandage was removed the skin was found to have healed over the wound, but a small haematoma about 2 mm. in diameter had formed. Day by day this increased in size until on the sixteenth day it was a swelling as large as a walnut. Fluctuation was readily elicited in it. By this time the skin had begun to split, and blood was oozing from a rupture in a fibrinous membrane which was thus exposed. An incision was made into the swelling, and after cutting through a tough layer of fibrin the central portion was found to consist of a loose clot, in the meshes of which there was much uncoagulated blood. The haematoma thus showed itself to be in reality a false aneurism, and the gradual increase in size to have been due to a slow stretching of the sac of fibrin by the pressure of blood from the severed arteriole, with which it was in direct communication. The loose central clot was due to partial secondary coagulation. All thrombin must long ago have disappeared from it, not only by attachment to fibrin but also by neutralization by anti-thrombin. It would never have grown any firmer, and it had no coagulating effect on fresh blood flowing through it from the cut vessel. Surrounding it on all sides and entirely cutting it off from contact with the tissues, and thus from all chance of the addition to it of thrombokinase, was the primary clot. It was extremely dense and firm, and was only separated from the tissues with some difficulty. After this had been done, a strong solution of human thrombokinase was applied to the raw area and continuous pressure kept up for some time. There was no further bleeding and rapid healing ensued.

This type of coagulation in a wound is the direct result of the great delay in the formation of thrombin. The primary clot is laid down very slowly and gradually, because it can only occur where the concentration of thrombokinase is very high. It thus comes about that at no time is there a sufficient amount of thrombin liberated from it to produce complete secondary coagulation in the rest of the blood. In a person in whom the coagulation time of the blood is normal, as has been shown, thrombin rapidly forms in the presence of much smaller quantities of thrombokinase than are necessary to produce thrombin from haemophilic blood within a reasonable time. The primary clot is thus

much larger, and an amount of thrombin is immediately set free from it which is more than enough to cause complete coagulation of the remaining blood.

But although it may be granted that the deficiency in the coagulability of the blood is sufficient in itself to explain the phenomena observed in the persistent or recurring haemorrhages from wounds which are seen in haemophilia, are there no other clinical manifestations of the disease which seem to point to the existence of some further factor in the causation of the condition? It may be said, for example, that the very slight degree of trauma which will produce extensive bruises, or large effusions into joints in severe cases, is an occurrence which requires some further explanation than any mere fault in the blood itself. For before haemorrhage can occur there must be a lesion of the vessels. Surely the varying degrees of trauma which suffice to produce bruising in cases in which the condition is present in a severe, moderate, or slight form, point to a varying liability to rupture in the capillaries? It is true that there is no histological evidence of the presence of any constant or characteristic change in the walls of the vascular system in haemophilia, but an undue fragility of the capillaries might well exist, although it was not marked by any change in their microscopical appearance. Fragility of the capillaries is in itself an undoubted cause of haemorrhage. It is not uncommon to meet with people in whom bruising is very easily produced, although the coagulability of their blood is entirely normal.

But this assumption has been experimentally negatived by Morawitz and Lossen. By connecting a cupping-glass with a mercurial manometer they were able to determine the average amount of negative pressure which was required to produce bruising in normal individuals, and it was found that just as great an amount of suction was necessary to lead to bruising in Case VII, who has been classified here as a severe case of haemophilia, and who bruised very easily with any direct trauma.

Besides, the existence of any other factor than deficient coagulability is not necessary to explain these haemorrhages after very slight injuries. The feeling that there must be some other cause is at root due to the very widely spread idea that haemophilia is a disease in which haemorrhage is produced more easily than in healthy people, whereas in reality it is not. The real distinction between a haemophilic and a normal person is not in the occurrence but in the *amount* of the bleeding. A normal person sustains a slight blow on the arm. A few capillaries are ruptured, but they are sealed almost at once by coagulation, and there are no signs of bruising. A similar degree of violence applied to a haemophilic will not lead at the moment to any greater haemorrhage; the difference arises later when haemorrhage continues for some time, so that such an amount of blood enters the tissues that signs of bruising appear.

Bleeding into a joint is often followed by a subacute inflammatory condition of the synovial membrane. Haemorrhage then arises with lesser degrees of trauma than are necessary when the membrane is healthy, and so it comes about that effusion may be produced into the joints of a haemophilic by

accidents, so trivial that they would not lead to any bleeding at all in a healthy joint. But the minimal degree of trauma necessary to cause haemorrhage into such a haemophilic joint will also lead to bleeding into the joint of a normal person in which there is an equal amount of synovial irritation. The end result will be different. In the haemophilic there will be a visible effusion, and in the normal person there will be no signs of haemorrhage. The distinction lies in the longer continuance of the haemorrhage in the one case than in the other, and not in its original inception.

The other theories of haemophilia, such as that it is due to disproportion between the quantity of blood and the size of the vessels, or that it is a manifestation of an organismal infection, &c., have been criticized by Sahli. They are for the most part purely speculative in character, and no practical evidence has been adduced in favour of any of them. For this reason, and in view of the positive evidence presented here, hereditary haemophilia is concluded to be directly due to a deficiency in the coagulability of the blood.

That is the opinion which all those who have worked at the subject in recent years already hold,<sup>9</sup> and I have merely endeavoured to present a few further points in its support, for it is a matter of more than theoretical interest, since it raises the hope that researches into the cause of this defect in coagulation may yield knowledge on which an efficient treatment of the disease may be based. My thanks are due to the patients who, sometimes at the cost of some personal inconvenience, allowed these observations to be made.

### *Conclusions.*

- I. There is a deficient coagulability of the blood in each case examined.
- II. The degree of the defect in coagulation corresponds with the degree of the severity of the clinical symptoms.
- III. The coagulation of blood flowing from a wound is induced by thrombokinase added to it from the tissues, and the rapidity of coagulation varies directly with the amount of this thrombokinase. Much larger quantities of thrombokinase are required to produce rapid clotting in haemophilic than in normal blood. In a wound in a haemophilic, coagulation may therefore only occur in those parts where the concentration of thrombokinase is highest, i. e. on the sides of the wound. But this clot prevents the addition of further quantities of thrombokinase from the tissues, and when the amount of thrombin liberated from the primary clot is insufficient to lead to the complete coagulation of the blood in the centre of the wound, bleeding may continue indefinitely.
- IV. Haemorrhage is no more easily induced in a haemophilic than in a normal person. The distinction is not in the occurrence but in the amount of bleeding.

<sup>9</sup> Nolf and Herry must be excepted from this statement. In a paper published this year they revert to the idea of a special friability of the capillaries, believing that the delay in coagulation is not sufficient to explain the internal haemorrhages and the easily produced bruising in haemophiles.

*The Cases investigated.*

*Case I.* Male, aged 51. In his youth especially, he had suffered from all varieties of haemorrhage, for which he had been admitted to hospital no less than twenty-seven times, but for a number of years he had been entirely free from symptoms, so that shortly before I saw him he had ventured to have a tooth extracted. Serious haemorrhage followed and continued for ten days. He had two first cousins on his mother's side of the family who were haemophilics. One of them had died of haemorrhage.

*Case II* is a first cousin of *Case V*, and is a middle-aged man. He had had to be admitted to the hospital on seven occasions for continued haemorrhage, but for a long time he had not had haemorrhages. He considered himself to be quite cured.

*Case III* was nineteen years old. He was the brother of *Case IV*, and the first cousin of *Case V*. So far as he knew the disease first became apparent when he was eighteen months old. This is a history which appears to be often given, and on this ground it has been supposed by some that the condition only develops some time after birth. But this freedom from symptoms during the first year is probably due to the care with which babies are handled. Dr. Nacke of Kirchheim told me that he could usually say at birth which members of the Mampel family were going to be haemophilics from the bleeding from the cord, which continued in them even after it had been firmly ligatured. Several cases had died of such haemorrhages. This particular case was seldom free from an effusion into one or other of his joints. He had had several severe and dangerous haemorrhages, notably one from a cut on the scalp which bled for a fortnight.

For *Cases IV and V* I am indebted to Dr. Groves of Bristol, who has already published an account of their personal and family history in a paper on some of the surgical aspects of haemophilia. They were both cases with well-marked symptoms.

*Cases VI, VII, VIII, and IX* were members of the famous haemophilic family of Mampel, most of whose descendants still live in the village of Kirchheim near Heidelberg. The story of this family has been written several times in the last fifty years. The most recent account is by Lossen, who gives a family tree which goes back for many generations.

*Case VI* was a middle-aged man in whom the improvement which sometimes comes when youth is past was scarcely perceptible, although on the whole he considered himself to be rather better than when he was young. He was seldom, however, free from bruises, effusions into the joints, or bleeding from the gums. While he was under observation he suffered from an effusion into one of his elbow-joints and from several bruises following on trifling injuries.

*Case VII* was the boy on an examination of whose blood Morawitz and Lossen based their paper on the causation of the deficient coagulability in haemophilia. They give a full clinical history.

*Case VIII* was eleven years old and had a very similar history to his cousin, *Case VII*. Both were cases in which the symptoms were prominent.

*Case IX* was sixteen years old. At the time I saw him he was suffering mainly from recurrent attacks of haematuria. He had a deformity of the forearm similar to that described by Dr. Groves in *Cases IV and V*.

*Cases X and XI* were under the care of Dr. T. Y. Finlay, to whom I am indebted for the opportunity of observing them.

*Case X* was a severe case.

*Case XI*, who was from a different haemophilic stock, was the case described as being of only moderate severity.

I have to thank Mr. J. M. Cotterill for giving me facilities to investigate the coagulability of the blood in *Case XII*. The clinical history and an account of other investigations in this case will appear later. He was a middle-aged man in whom the evidence of a haemorrhagic tendency was very pronounced.

## REFERENCES.

1. Addis, *Brit. Med. Journ.*, 1909, i. 997.
2. Addis, *Edinb. Med. Journ.*, 1910, N. S. v. 38.
3. Addis, *Quart. Journ. Exper. Physiol.*, 1908, i. 305.
4. Baum, *Mitt. aus den Grenz. der Med. u. Chir.*, 1909, xx. 1.
5. Dalghren, *Beiträge zur klin. Chirurgie*, 1909, lxi. Feb. 3.
6. Groves, *Brit. Med. Journ.*, 1907, i. 611.
7. Kottmann u. Lidsky, *Münch. Med. Woch.*, 1909, lvii. 1. 113.
8. Lossen, *Deutsch. Arch. f. Chir.*, 1905, lxxvi. 1.
9. Mellanby, *Journ. Physiol.*, 1909, xxxviii. 28.
10. Morawitz u. Lossen, *Deutsch. Arch. f. klin. Med.*, 1908, xciv. 110.
11. Nolf et Herry, *Revue de Méd.*, Paris, 1909, xxix. 841 ; 1910, xxx. 19 and 106.
12. Rettger, *Amer. Journ. Physiol.*, 1909, xxiv. 406.
13. Sahli, *Zeitschr. f. klin. Med.*, 1905, lvi. 264.
14. Weil, *Bull. et Mém. de la Société médicale des hôpitaux de Paris*, 1908.
15. Wright, A. E., *Allbutt and Rolleston's System of Medicine*, Lond., 1909, v. 929.

# A FURTHER NOTE ON HAEMATOPORPHYRINURIA NOT DUE TO SULPHONAL<sup>1</sup>

By T. K. MONRO

It has been remarked that haematoporphyrinuria, as shown by the work of Garrod and others, presents itself under three aspects: (1) Haematoporphyrin in minute quantity is a normal constituent of healthy urine; (2) It is often present in increased quantity in disease without any noteworthy change in the colour of the urine; (3) It may be present in great excess in urine whose colour is abnormal—pink, red, magenta, brown, or almost black. The third class of cases, just described, falls into two groups: (a) In the larger group the haematoporphyrinuria is a result of intoxication by a drug, such as sulphonal, trional, or tetronal; (b) In the smaller group no drug can be incriminated, but the haematoporphyrinuria may be associated with various other morbid states, or may be persistent during many years, or may be intermittent or paroxysmal like paroxysmal haemoglobinuria.

Now it has been shown by Hammarsten that these abnormally coloured urines contain other abnormal pigments besides haematoporphyrin; by Sobernheim that the haematoporphyrinuria may persist after the abnormal colour has almost disappeared; and by Garrod that the haematoporphyrin may be removed from a urine of this kind without materially altering its colour, and that a corresponding amount of haematoporphyrin may be added to a normal urine without producing any great change in its appearance. The obvious inference is that the red, brown, or other abnormal colour of the urine in cases of so-called 'haematoporphyrinuria' is not due to haematoporphyrin itself but to some associated pigment.

There are therefore (a) cases in which an excess of haematoporphyrin and a pigment giving an abnormal colour are both present; and (b) cases where an excess of haematoporphyrin is present without the unusual pigment. This being so, it is reasonable to expect that (c) cases will be met with where the abnormal pigment is present in the urine and yet without excess of haematoporphyrin. The case which follows appears to be one of this kind.

I am not sure that the subject has been considered in the literature exactly from this point of view, but I understand from Dr. Garrod that the phenomenon in question is not unknown to him. Dr. Garrod was kind enough to call my attention to a case put on record by Schölberg in the *Transactions of the Pathological Society of London* for 1901–2 (vol. liii), but in this instance the urine was of natural colour on passing and became purple only on standing. The peculiarity was apparently congenital, and was present in other members of the family. It is possible that a brown pigment described by Thiele in the

<sup>1</sup> See this *Journal*, 1907, i. 49.

pages immediately preceding Schölberg's communication, and not characterized by any spectroscopic band, is more akin to the one I am about to describe.

*Case.* On the morning of Sunday, June 13, 1909, a lady, aged about 34, who was within a few days of her first confinement, called attention to the remarkable colour of her urine. The urine had been repeatedly tested before and found normal. She had been vomiting once in the twenty-four hours, usually shortly after going to bed, but in the main her health was excellent, though for some time she had suffered from attacks of neuralgia, which came on in the middle of the night and involved the head generally.

On Saturday, June 12, she had been examined about midday by the medical man who was to attend her in her confinement. She noticed that night at bed-time, for the first time, that the urine looked like blood, and she naturally attributed this to the medical examination, since the latter had been painful. Urine with the same appearance was passed on the Sunday morning. She never noticed such urine except on these two occasions. In the middle of that night, i. e. after the first abnormal specimen had been passed, she had neuralgia, and took phenacetin and acetyl salicylic acid (10 grains of each). She had not been taking any medicine of late except liquid extract of cascara.

I thought I had come across another case of haematoporphyrinuria not due to drugs, but this proved to be a mistake. The urine was of a bright blood-red colour, with a trace of brown when looked at in certain ways; quite transparent; no sediment or turbidity of a kind that could suggest blood; specific gravity 1032; no albumin; guaiac test for haemoglobin negative; no sugar; nitroprusside test for acetone negative. Perchloride of iron gave a dark purplish, almost black colour.

As Dr. Riddell, who examined the former specimens for me, was not at hand at the time, I sent this one to Professor Carstairs Douglas, of the West of Scotland Clinical Research Laboratory. The result of a thorough investigation was that no haematoporphyrin could be detected in the urine. Neither was there any evidence of urobilin.

*Report by Professor Douglas (June 15, 1909).*

'I have carefully examined the specimen of urine... but cannot satisfy myself that this is a case of haematoporphyrinuria. The sample was in part acidulated with acetic acid, and thoroughly extracted with amylic alcohol, but yielded no spectrum of haematoporphyrin; nor on the addition of ammoniacal zinc acetate did it show any fluorescence, as it would have done had urobilin been present. It gave no red precipitate (Riva and Zoja) as haematoporphyrin does. The dark pigment was not extracted by amylic alcohol, nor by ether or chloroform. I then tried Salkowski's plan of precipitating the pigment along with the urates, phosphates, and sulphates by adding to a fresh portion barium hydrate solution and barium chloride, filtering, and washing the precipitate with water, then alcohol, and dissolving with hydrochloric acid and alcohol. This also failed to extract any haematoporphyrin. The dark pigment was left entirely untouched by this procedure, and the filtrate from the barium treatment... looked practically unchanged.

'It is not bile, but is that unidentified pigment not unfrequently met with in cases of haematoporphyrinuria.'

## TWO CASES OF ACUTE ENDOCARDITIS

By JOHN COWAN, A. M. KENNEDY, A. R. PATERSON,  
AND JOHN H. TEACHER.

With Plates 2 and 3

IN a recent number of this Journal,<sup>1</sup> two of us reported a case of partial heart-block, occurring during an attack of acute rheumatism and persisting for a fortnight; and we suggested that the condition might be due to the involvement of the *a.-v.* bundle in one of those little inflammatory lesions which are so frequently present in the myocardium in the acute infections. The favourable issue of our case precluded confirmation of our theory, but we have again met with cases where it seemed probable that the *a.-v.* bundle or node was implicated in the way which we had suggested, and in two of them we were able to secure a microscopic examination of the parts.

Our first case was a man aged 26 years, who was admitted into hospital on June 5, 1909, complaining of weakness and of breathlessness on exertion of some months' duration. He stated that he had not been in good health since an attack of enteric fever in 1903 for which he was in hospital in Japan for about three months. He never regained his former health, and his feet were often swollen at night, but he was able to work as a clerk until July, 1908, when he was thrown out of employment by the failure of his firm. He stayed at home in fairly comfortable circumstances until he procured a new situation on February 19, 1909. In the early part of February he had caught cold and he was feeling 'run down' when he commenced his new work. This entailed a daily walk of four miles, and he felt exhausted at night, and also during the day when walking uphill, but though he steadily became weaker he continued at his post until six weeks before admission, when he was compelled to go to bed. His cough, accompanied by a slight mucoid spit, persisted from February until May. He had frequent attacks of shivering at night after getting home; they were fairly severe, and lasted for fifteen to twenty minutes, and he felt hot after he got into bed, and often sweated profusely in the early morning. About a fortnight before admission his right forearm and elbow became sore to the touch and on movement, and this continued for a few days. Four days before admission the left hip and ankle became painful, and this still persisted.

His family history was good. He had always been healthy prior to 1903, but he admitted on cross-examination that he had suffered from growing pains and an attack of tonsillitis in boyhood. He had also had an attack of gonorrhoea early in 1903. On admission he was found to be a thin, pale, badly nourished man, with flabby muscles and little subcutaneous fat. The left hip and ankle were painful and tender, and there was a small

<sup>1</sup> 1910, iii. 115.



tender area of induration on the back of the left forearm. The right calf was, he said, painful, but it seemed normal on examination. There were several minute ecchymoses on the conjunctival surface of the right lower eyelid, and a fairly large one on the conjunctiva of the left bulb, while ophthalmoscopic examination revealed a medium-sized flame-shaped haemorrhage on the course of the left superior temporal vein (A. J. Ballantyne). The lungs were normal, the tongue was clean and digestion good; the liver and spleen were slightly enlarged; the urine contained a small amount of albumen. The heart was but little enlarged, though there was a well-marked mitral systolic murmur. The pulse was frequent, regular, small, and soft; and he was slightly fevered at night.

Progress after admission was slowly but continuously in the wrong direction. Many embolisms occurred, chiefly in the limbs, but once at any rate in the spleen, and twice in the kidneys. He had several 'faint turns' of a few minutes' duration without obvious cause. The weakness increased, and after the middle of July oedema was more or less continually present in the legs. There were occasional rigors, and generally profuse sweats at night. On August 25 a left hemiplegia occurred, and he died on August 29.

*Post-mortem* examination revealed an acute endocarditis of the mitral valve. Two emboli were present in the right middle cerebral arteries, and septic infarctions were present in the left kidney and the spleen; from the latter the pneumococcus and *B. coli communis* were isolated on culture. Blood cultures during life had proved sterile.

The mitral valve was dilated. Numerous vegetations were present on the cusps, some small and wart-like, others long and luxuriant. The endocardium of the left auricle was thick and opaque, and a few minute granulations were present on the contra-fossal wall, immediately above the valve: the endocardium at this point was notably thickened. There was no evidence of mural implication elsewhere.

A block of tissue containing the auriculo-ventricular bundle and node was embedded in paraffin and cut in serial sections on a plane at right angles to the long axis of the heart (A. M. K.). Microscopic examination revealed well-marked congestion of both node and bundle. The node was otherwise normal, though two small foci of round cells were found in the auricular muscle in its immediate vicinity. The bundle was involved in three separate places by foci of the same kind. The first was of small size, and was situated immediately below the node; the second, which was considerably larger, was found a little lower down, between the auricular muscle and the bundle, and implicated both; the third, of fair size, occupied the central part of the bundle, and occurred immediately above the point where it passed through the central fibrous body. The cells in the foci were all mononuclear, and the majority were evidently lymphocytes. A few larger cells with a fair amount of protoplasm were also present, and were probably of connective tissue origin. The fibres of the *a.-v.* bundle seemed normal, save in the immediate vicinity of the two larger foci, where they were evidently degenerate. The fibrous tissue of the bundle was not excessive in amount. The cardiac muscle generally showed evidence of interstitial myocarditis in an early stage, and the muscle fibres in some of the patches were degenerate.

The pulse during the patient's residence in hospital was always regular, until immediately before death; and the venous curves were normal, save that

the *a-c* interval was invariably prolonged, measuring about 0.25" and never touching 0.2" or 0.3".

The little lesions which are present in the bundle seem sufficient to account for the trifling delay in the conduction of the stimulus from auricle to ventricle.

The second patient was a van-driver aged 24, who was admitted into hospital on July 15, 1909. On July 1 he had had one of his right upper molars extracted on account of a gumboil from which he had suffered for a day or two. In the evening he felt sick and shivery, and probably was fevered. These symptoms continued, and on the afternoon of July 4 he had a definite rigor. On the 7th he felt better, and on the 8th he went to Ardrossan, walking from the station to the house at which he stayed (2 miles). After this he improved until the 12th, though he had a slight cough after the 6th, with discomfort in the left chest. But on the 12th he had to go to bed as the pain in the side became worse, and was much intensified on coughing. The left arm, too, was stiff, and he was very breathless and had to sit up in bed at night. On the evening of the 13th he was better, and able to sleep quietly lying down.

On July 14 he felt so well that he dressed and went downstairs to breakfast, which he did without any difficulty or assistance; after breakfast he sat down in a chair, and on attempting to rise an hour later found that his legs were powerless, and 'had no feeling' in them. He had to be carried back to bed. In the evening he felt 'pins and needles' in the right leg.

His previous health had been good, save for attacks of measles and enteric fever in childhood; but he was often troubled with gumboils, and was frequently wetted at his work. His family history was unimportant.

On admission he was found to be notably emaciated, with small muscles and scanty subcutaneous fat. His complexion was somewhat sallow, and his expression anxious, while he had to be propped up in bed on account of breathlessness. There was a large fixed antero-posterior curvature of the spine with the maximum curve about the ninth or tenth dorsal vertebra, which he stated had been present for about eight years. The respirations were both thoracic and abdominal, the expansion of the chest being poor (1"). The skin was hot and dry, and there was a little oedema of the feet, and slight pitting with the stethoscope on auscultation over the cardiac area. He was slightly fevered at night. The patient, though weak, was quite clear mentally, spoke correctly, and answered questions accurately and sharply. He had little power in his legs, but was able to pull up both knees, though he was unable to move the toes of the right foot. The movements were more free on the left side. There was considerable anaesthesia in both legs, the right leg being insensitive to touch as high up as the groin, the left half-way up the thigh: painful stimuli were appreciated correctly in the left leg above the ankle; in the right they were only felt as contacts and that after an appreciable delay. Thermal sensations were appreciated correctly in the left leg. Power was perhaps deficient to some slight extent in the left arm, but in the right was good; and sensation seemed normal. The plantar, cremasteric, and abdominal reflexes were absent, and the knee-jerks could not be elicited. The epigastric reflexes were present and equal. The flexor jerks in the arms were present and equal, and the jaw-jerk was present. The right pupil was slightly smaller than the left; both reacted to light and on accommodation.

The patient had control over his bladder, and testicular sensation was normal. The tongue was dry and coated, many of the teeth were absent, and most of the remainder were carious, and the mouth generally was very foul. The pulse was soft, regular and infrequent. Palpation of the apex beat, which was full and widespread, showed that every other beat was missed at the radial, the cardiac action being regularly coupled. A systolic murmur was audible all over the cardiac area. It was heard best at the apex, where it was long and

soft, replacing and running out of the first sound; the second sound was not audible here. The respirations were difficult and cyclic, but without any full apnoea. The upper part of the right chest was dull on percussion, and the respiratory murmur here was deficient, with prolongation of expiration. In the left lower axilla friction sounds were audible; the stools contained a little mucus. The urine was concentrated and dark in colour, and contained a trace of albumin.

For a few days his general condition improved slightly. The coupled rhythm ceased on the 16th, and he rested fairly well at night. The sphincter ani was flaccid, and he had no control over the bowels, though micturition was normal. On the 17th movement was more free in the left leg, but the palsy below the right knee persisted. Anaesthesia was still present, but did not extend so far up on the left leg, being apparently normal above the knee. The left plantar reflex and knee-jerk had reappeared, but the right were still absent.

About midnight on the 18th he was noticed to be restless, and was found to be semi-conscious and unable to say more than 'yes', and there was a well-marked full right hemiplegia. He gradually became weaker and more comatose, and the respirations and pulse became more frequent. Râles appeared all over the lungs, and he died with cardiac failure on July 27, 1909. The pulse remained 'single' until the day of death, when it was noticed to be 'coupled' again for a short time.

*Post-mortem* examination revealed an acute ulcerative endocarditis of the mitral valve, engrafted on a lesion of old standing. The upper and middle lobes of the right lung were solid from a somewhat chronic pneumonia, and there were numerous infarcts in the spleen and kidneys. The left middle cerebral artery was occluded by a large pale embolus which resembled the vegetations on the mitral valve, and was associated with a very extensive softening which involved the lenticular and caudate nuclei, most of the internal capsule, the island of Reil, and a large portion of the central convolutions; the rest of the brain and the spinal cord seemed normal. Microscopic examination of the cord showed no evidences of local damage (J. H. T.). Streptococci were isolated on culture from the spleen. No blood cultures were made during life.

The mitral valve was stenosed, the cusps being notably shortened, the chordae tendineae short and thick, and the tips of the papillary muscles fibrous. There was well-marked evidence of fibrosis spreading upwards from the bases of the cusps in the direction of the central fibrous body of the heart. Enormous soft recent vegetations almost occluded the valve, and there was in addition extensive ulceration and perforation of the anterior mitral cusp. There was no evidence of any acute mural endocarditis; but the endocardium of the left auricle was thick and opaque, with a special area of thickening about as large as a shilling on the contra-fossal wall just above the valve.

A block of tissue containing the auriculo-ventricular bundle and the node was embedded in paraffin, and cut in serial sections on a plane at right angles to the longitudinal axis of the heart (A. M. K.). Microscopic examination revealed considerable congestion of the tissues generally. The node was the site of a profound inflammatory disturbance, many focal collections of round cells being present, as well as, in places, a diffuse infiltration. The bulk of the cells were lymphocytes, but a few large mononuclear cells, both round and spindle-shaped, were also present. The fibres of the *a.-v.* node were probably normal, and there was no evidence of old-standing fibrosis. The walls of a microscopic artery (Plate 3, Fig. 2) were infiltrated with round cells, though the lumen was patent; the other vessels seemed normal. The intensity of the lesions varied at different levels, but the whole of the node was more or less affected. The bundle, on the

other hand, was not implicated, save at one place immediately below the node, where one or two small foci in the auricular muscle immediately adjoining it passed in for a short distance between a few of its fibres.

There was a well-marked myocarditis, involving both ventricle and auricle, but it was only extreme at the base of the mitral valve, and in the auricular sections immediately above the node itself.

The tracings which were obtained in our second case differ from those in our first. The early tracings are somewhat difficult to interpret and are discussed in detail elsewhere.<sup>1</sup> In the last tracing which we obtained, with a 'single' rhythm, the *a-c* interval is apparently very short, measuring little more than 0.05".

During the *a-c* interval five events occur: (1) the auricular systole; (2) the passage of the stimulus from auricle to ventricle; (3) the latent period; (4) the period of ventricular systole prior to the opening of the aortic valves; (5) the transmission of the aortic wave to the carotid artery. The normal *a-c* interval measures about 0.2", being somewhat shorter in a quickly beating heart, the auricular systole lasting for nearly 0.1", and the period between the commencement of the systolic rise on the apical tracing and the carotid wave in the jugular pulse measuring about 0.05". An *a-c* interval of 0.1" is almost certainly, and an interval of 0.06" is surely, too short to permit the normal sequence of events, and it seems probable that the shortness of the interval is due to the more or less synchronous contraction of auricle and ventricle. A single large wave not infrequently occurs in the jugular curve synchronous with the occurrence of the carotid wave (the 'nodal' extra-systole of Mackenzie), and is usually considered to be the result of auricular contraction at a time when the auriculo-ventricular valves are shut. From our previous argument it is evident that in Mackenzie's 'nodal' extra-systole the ventricle must have contracted before the auricle, for otherwise the delay in the appearance of the carotid wave would produce a carotid elevation subsequent to the auricular wave. If a period of between 0.05" and 0.1" elapses between the auricular and the carotid waves in the jugular curve it seems probable that the contractions commence simultaneously in both auricle and ventricle.

Conclusions of this kind have for some time been floating in the minds of those who are interested in cardiac work (Mackenzie, Hay, Ritchie), and it is extremely interesting to find that in our second case, where the clinical evidence is in favour of the theory that the auricular and the ventricular contractions commenced simultaneously, the pathological lesion is almost wholly confined to the *a.-v.* node, and the stimulus probably originated at this level. But we must not forget that our theory makes a lesion in the *a.-v.* bundle in one case responsible for a defect in function, and a lesion in the *a.-v.* node in our second case a cause of increased irritability.

We can find but few records in the literature of systematic examination of the 'primitive tissue' of the heart. Mackenzie, however, reports two cases

<sup>1</sup> Cowan and Ritchie: Coupled Rhythms of the Heart-case, below, p. 66, Case VII.

where it was involved by lesions of the kind which we have described : (1) a case of cardio-sclerosis with 'nodal' rhythm for two months before death ; the *a.-v.* node and bundle were affected ; (2) a mitral case, with attacks of paroxysmal tachycardia ; here the sino-auricular node was involved as well as the *a.-v.* node and bundle. Schönberg reports five cases of persistent irregularity of the heart in which the sino-auricular node was affected : the *a.-v.* bundle and node were not examined. Vaquez reports a case of paroxysmal tachycardia in which the sino-auricular and *a.-v.* nodes and the *a.-v.* bundle were involved.

The sensory disturbance in the left leg raises a question of great interest, for the only lesion found in the central nervous system was confined to the left cerebral hemisphere. The sensory disturbance was noticed on July 15th, 16th, and 17th, but could not be followed after the 19th on account of the mental disturbance produced by the second embolus. The area involved was diminishing on the 17th.

It is, of course, well known that unilateral cerebral lesions produce relative weakness of the muscles on the same side as the lesion, as well as palsy on the opposite side, but there are few cases on record of bilateral sensory loss. A recent paper by G. Bergmark contains, however, four cases, two of which were observed by himself. His first case was a man aged 66, who developed a right hemiplegia on March 6. Two days later there was complete right hemianaesthesia and 'marked hypalgesia of the left lower extremity', which had disappeared three weeks later. His second case, a man aged 74, developed a left hemiplegia in September ; when examined four months later, the right leg below the knee and the distal phalanges of the right finger were insensitive to cotton-wool touch. *Post-mortem* examination revealed an extensive lesion occupying almost the whole of the internal capsule, the greater part of the lenticular nucleus, and the external and lower portions of the optic thalamus. He quotes two cases, recorded by Freidrich Müller, with hypalgesia in the distal part of the lower extremity on the non-paralysed side.

The cause of the bilateral loss is somewhat obscure. Bergmark rejects the obvious theory of bilateral innervation proposed by Müller, as he found that in his first case defective sensation in the mesial parts of the trunk on the non-paralysed side disappeared rapidly, while that in the legs lasted for longer and disappeared simultaneously. He thinks that a more plausible explanation can be found by assuming a double cerebral lesion, that in the 'healthy' hemisphere being relatively slight and transient, and the result of the disturbance of the cerebral blood supply.

The rarity of bilateral sensory disturbances is probably more apparent than real, for it is but seldom that sensation can be accurately tested immediately after the occurrence of a cerebral lesion, as the disturbance of cerebral function commonly affects the intelligence of the patient and affords obvious sources of inaccuracy ; and the sensory loss is often transient.

## CONCLUSIONS.

Microscopic examination of the  $\alpha$ -v. node and bundle in two cases of acute endocarditis revealed well-marked inflammatory lesions in the parts. In one case, where the  $\alpha$ -c interval in the jugular curve was prolonged, the lesions implicated the bundle; in the other, where the  $\alpha$ -c interval was very short, the node alone was affected.

## REFERENCES.

1. Bergmark, G., *Brain*, 1910, xxii. 342.
2. Cowan, M'Leod, and Paterson, *Quart. Journ. Med.*, Oxford, 1910, iii. 115.
3. Mackenzie, James, *Diseases of the Heart*, Lond., 1908, 309, 315.
4. Schönberg, S., *Frankfurter Zeitschr. f. Pathol.*, 1908, ii. 153.
5. Vaquez, H., *Archives des Mal. du Cœur*, Paris, 1909, ii. 609.

## DESCRIPTION OF FIGURES.

*Case I.*

PLATE 2, FIG. 1. Tracing showing a slight delay in conduction.  $a-c = 0.25''$ .

FIG. 2. Diagram showing the situation of the microscopic lesions in the *a.-v.* bundle.

FIG. 3. Microphotograph of lesion no. 1.  $\times 90$ . A small round-cell collection is shown in the substance of the *a.-v.* bundle (1). (2) is the central fibrous body of the heart.

FIG. 4. Microphotograph showing lesion no. 2.  $\times 90$ . A round-cell collection is visible between the auricular muscle (2) and the *a.-v.* bundle (1), and infiltrates both. The *a.-v.* bundle here is congested, and its fibres are degenerate.

FIG. 5. Microphotograph showing lesion no. 3.  $\times 90$ . A larger round-cell collection is shown in the centre of the *a.-v.* bundle (1). (2) = auricular muscle. The *a.-v.* bundle here is congested, and its fibres are degenerate.

*Case II.*

PLATE 3, FIG. 1. Tracing showing the close proximity of the *a.* and *v.* waves in the jugular pulse.  $a-c = 0.06''$ .

FIGS. 2-4. Microphotographs of the *a.-v.* node at different levels, showing focal and diffuse round-cell infiltrations. The artery in Fig. 2 is *not* thrombosed: it is cut obliquely and its walls are infiltrated. All the capillaries are congested.

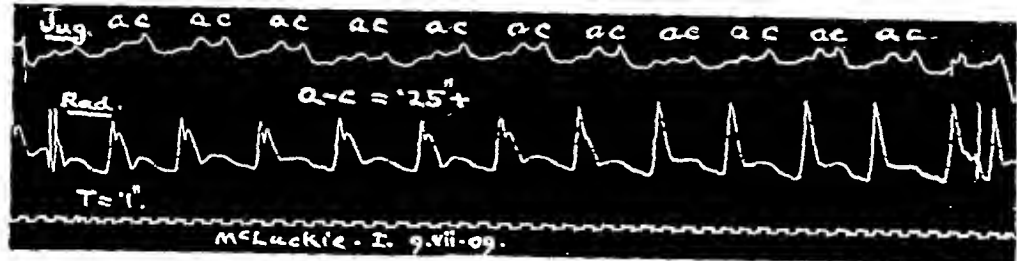


FIG. 1

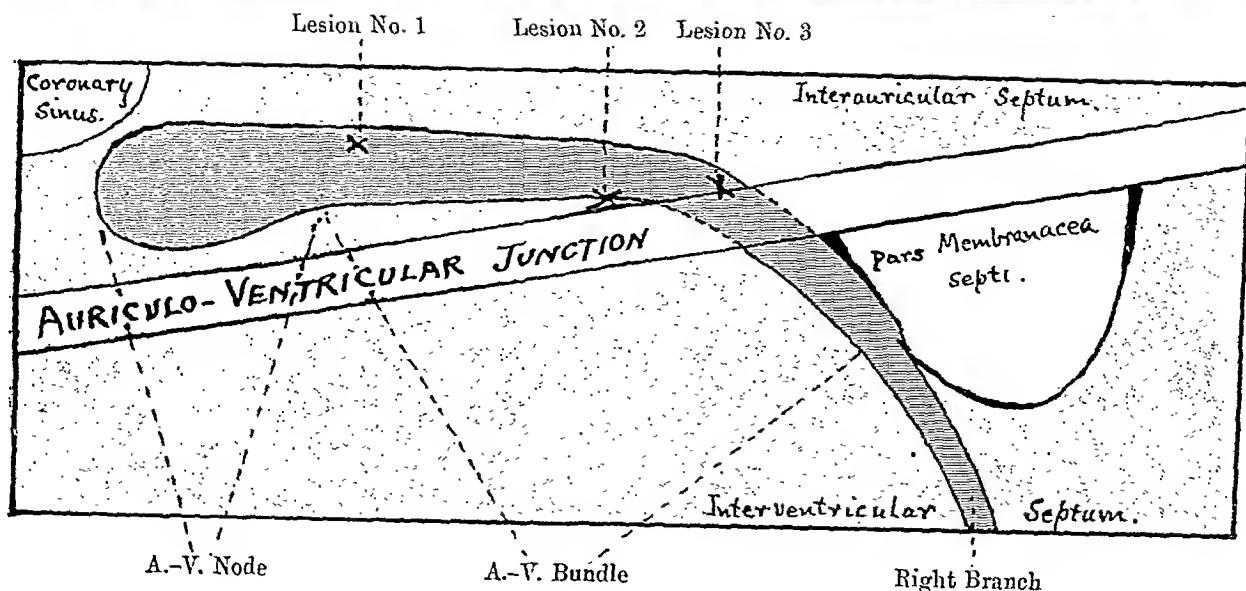


FIG. 3

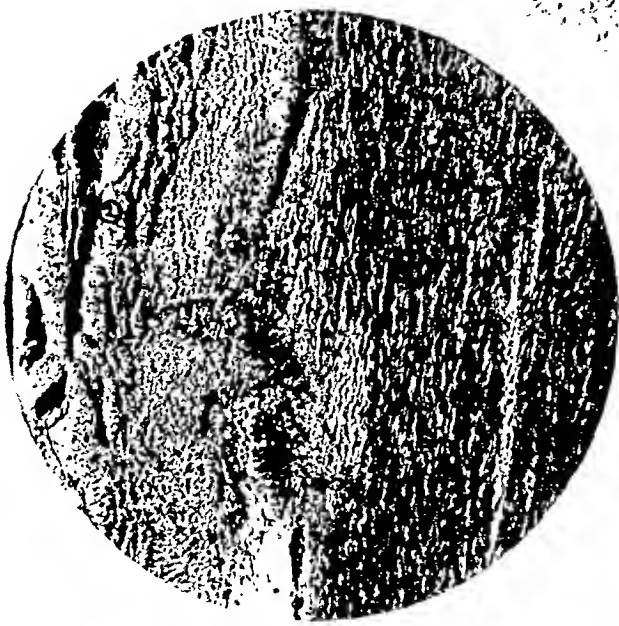


FIG. 4

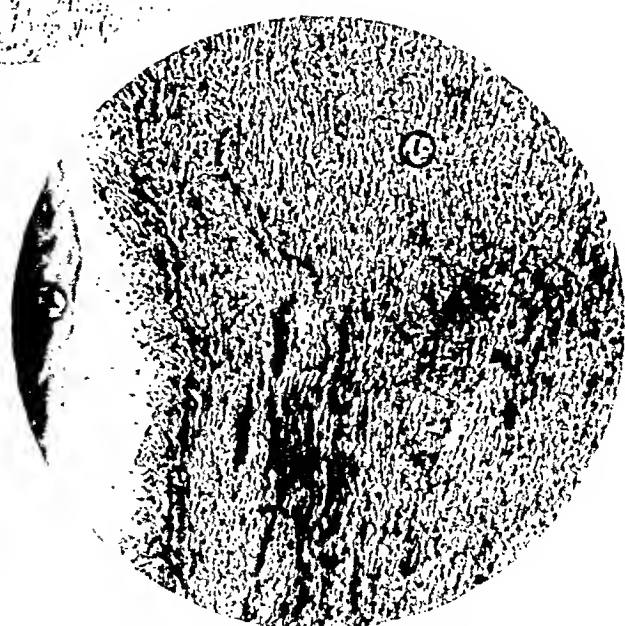


FIG. 5





CASE II

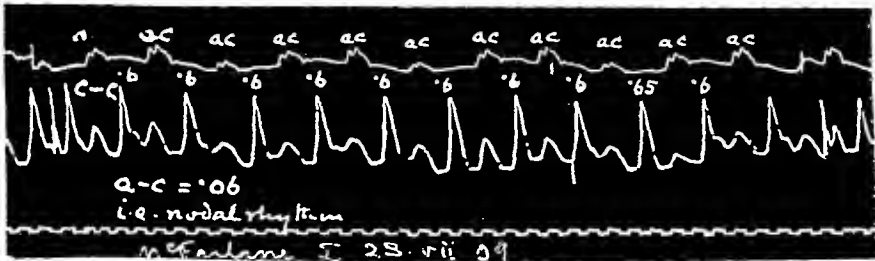


FIG. 1

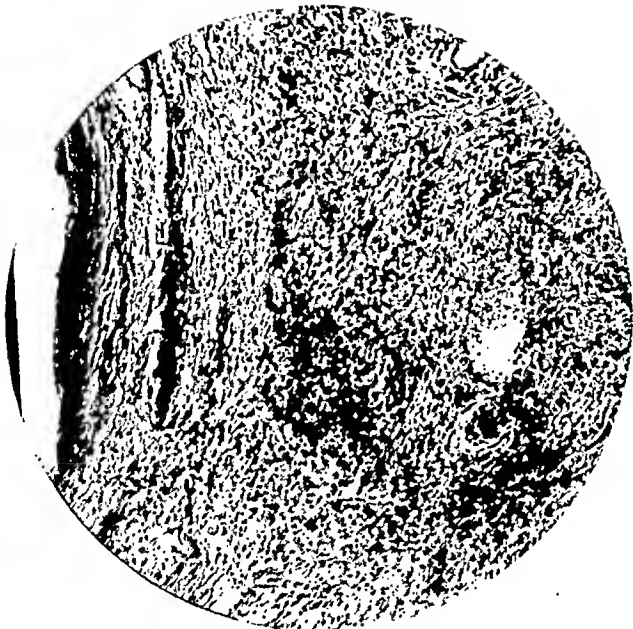


FIG. 2. Section 266

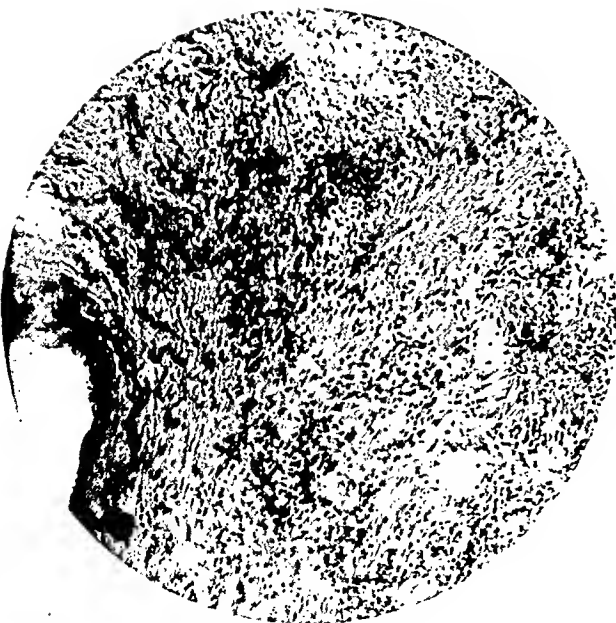


FIG. 3. Section 268

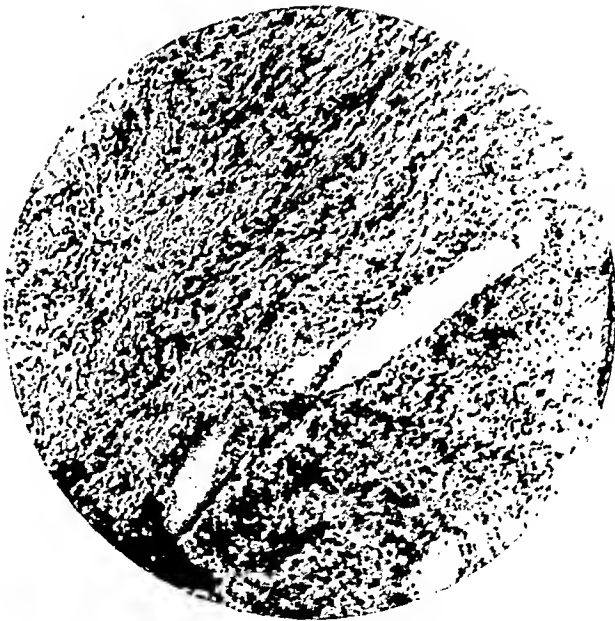


FIG. 4. Section 271



## TUBEROUS (TUBEROSE) SCLEROSIS

BY J. S. FOWLER AND W. E. CARNEGIE DICKSON

With Plates 4-6

TUBEROUS or nodular sclerosis is a rare developmental disease, which was first described by Bourneville so far back as 1880. It is of considerable interest, both pathologically and clinically. From the pathological point of view, the interesting fact about the condition is that, in a very large proportion of cases, tumours of the heart, kidneys, and other viscera, and also of the skin, or of some of these structures, are associated with the peculiar form of sclerosis of the cerebral cortex which has given the disease its name. Less is known about its clinical manifestations, because the post-mortem examinations have, almost without exception, been made upon patients dying in institutions for the feeble-minded, and until comparatively recently the clinical study of mental defect has remained behind that of other branches of medicine. It is at present impossible, in the great majority of imbeciles, to predict during life what pathological lesion will be found after death, and accordingly tuberous sclerosis is of importance from the clinical point of view, because it constitutes a definite type of imbecility, and has already in one or two instances been correctly diagnosed during the lifetime of the patient. The credit of having drawn attention to the clinical features of this disease belongs in great measure to Vogt of Frankfort.

The case which forms the subject of this communication is as follows:—

Maggie R., aged one year, illegitimate, was admitted to the Royal Edinburgh Hospital for Sick Children on July 11, 1909, suffering from convulsions. She was the second child, the father being 24, and the mother 28, at the time of her birth. There is no neuropathic history on the father's side, and the mother is said to be a healthy woman. The child was brought up by her paternal grandparents, and had no illness of any kind until the night before admission to hospital, when she suddenly became convulsed, chiefly in the left arm and side of the face. The convulsions were associated with loss of consciousness, and continued with slight remission for several hours. Before the present illness nothing was noticed wrong with the child. Her grandparents said that she was bright, and laughed and played like a normal baby; she began to hold up her head at the third month, and could sit up by the sixth or seventh month. Could not walk; slept well, and was a very good child.

*On admission:*—A well-developed and fairly nourished infant. She was quite unconscious, and was suffering from clonic spasms of the left side of the face. Slight rigidity of the neck was present. Limbs flaccid; knee-jerks active; no Kernig. Pupils equal; left internal strabismus. No aural discharge. Head

and face normal; fontanelle not tense. Heart, lungs, and abdomen (except for some retraction), normal. Blood pressure 70; pulse 130, regular. Temperature 100°.

Soon after admission she vomited; remained in an apathetic condition, taking no notice of anything, but was able to swallow quite well.

July 12, the day after admission, lumbar punctured. The fluid did not escape under pressure; it was perfectly clear when first withdrawn, but in a few minutes it became filled with small shreds of lymph which gave it a milky appearance. It contained about 40 cells (mostly lymphocytes) per c.mm.

July 13. Child restless; no more fits. Lumbar punctured again. Fluid as before, but more lymphocytes; did not reduce Fehling. A provisional diagnosis of tuberculous meningitis was made.

July 14. Well-marked Kernig.

July 19. Since admission eight days ago there have been no further symptoms. The infant remains semi-conscious, paying no attention to her feeds, and does not recognize her friends. The temperature has gradually fallen. On lumbar puncture the cerebro-spinal fluid was found to contain very few cells, and this, together with the arrest of the symptoms, led us to suspend the diagnosis of meningitis.

July 24. Has improved slightly, and is now taking some notice of her surroundings. Fundi normal. No cells in cerebro-spinal fluid.

July 28. Temperature again up for the past two days. Some dullness at the right base, on exploring which pus containing pneumococci was obtained. The chest was drained, about 5 oz. of pus being removed. After this the child became more and more apathetic; the lung did not expand; a secondary staphylococcus aureus infection occurred; and she died on August 7.

*Synopsis of post-mortem examination* (performed thirty-six hours after death):—

The body was that of a small, poorly developed, much emaciated female infant. *Rigor mortis* was absent. The cranium was somewhat large in proportion to the face and body generally. There was an operation opening for the drainage of an empyema of the right side of the chest. Adenoma sebaceum was not present.

*Serous Cavities: Right Pleural Cavity:* the posterior vertical half of the cavity, from base to apex, was the seat of an empyema. This was unilocular, with free drainage through the opening, and there were firm fibrous adhesions cutting off the empyema area from the anterior portion of the pleural sac.

*Left Pleural Cavity:* there was no excess of fluid. Early acute pleurisy was present, with extreme congestion of sub-pleural vessels, especially marked over the base of the lung.

*Pericardium:* appeared normal.

*Peritoneum:* showed no excess of fluid. The mesenteric glands showed moderate general enlargement, but no naked-eye evidence of tuberculous caseation or of tumour growth.

*Heart:* in the wall of the right auricular appendix, towards its base, there were two hard, somewhat rounded nodules—the larger about the size and shape of a coffee-bean, and the smaller about the size of a split-pea. These were pale pinkish-grey in colour, several shades paler than the tint of the surrounding muscle, and in consistence and colour suggested the appearance of small myomata, such as are seen in the uterus, but without any of the fasciculation which gives to the latter their typical 'watered silk' appearance. Except for the presence of these nodules, the heart showed no other naked-eye abnormality.

*Right Lung:* was semi-collapsed from empyema, as above, there being a thick layer of purulent lymph over its posterior surface. On section, there was marked collapse, and, in the lower lobe, widespread acute broncho-pneumonia.

*Left Lung*: Acute pleurisy, as above, and, on section, bronchitis, with large areas of lobular collapse in the lower lobe posteriorly.

*Liver*: except for cloudy swelling, there was no obvious lesion.

*Kidneys*: ditto, there being no subcapsular or other tumours present in either organ.

*Spleen, Suprarenals, Thyroid, Thymus, and Pituitary* showed no obvious change.

*Brain*: on removing the skull-cap the brain was found to be slightly increased in size, and at first sight did not appear to present any very obvious abnormality (see Plate 4, Fig. 1); but, on more careful inspection, and especially on palpation, it was found that, scattered over the surface of the cerebrum, there were numerous nodules, varying from about the size of a pea to that of a small walnut, about a dozen or more being embedded in the surface of each hemisphere. These nodules were extremely firm, and their position could be determined most easily by running the fingers over the surface, the sudden transition from ordinary soft brain tissue to dense resistant nodules of almost stony hardness being very striking. In colour they were pearly white—exactly the tint of the ordinary white matter of the brain—and distinctly more opaque than the surrounding grey substance of the cortex in which they were embedded. The pia-arachnoid, which was thin and comparatively non-vascular, was not adherent over them, stripping easily from their surface. The general contour of the convolutions was not much disturbed by their presence, the only points noted being that, especially in the larger nodules, the affected convolutions were slightly thicker or broader than normal, and projected to a very slight but appreciable degree above the general level of the cerebral surface. A few of the smaller nodules, however, were slightly below the general level, and were slightly ‘operculated’ by the surrounding unaffected convolutions. Some of the nodules showed a moderate degree of umbilication, and other irregularities, which gave them a finely nodulated or granular appearance, whilst others, again, presented a perfectly smooth surface. On section, the nodules were situated mostly in the grey matter, but the larger of them also projected well into the subjacent white matter, which they closely resembled in colour, but from which they could at once be distinguished by their great hardness, and, on close inspection, by their more compact and homogeneous texture and comparative non-vascularity. These appearances suggested that the condition was a replacement or diffuse infiltration of the affected areas by some sclerotic process, rather than anything of the nature of syphilitic gummata or tuberculous nodules; and, moreover, they were pearly white in colour, and showed none of the yellowish tint and cheesy appearance typical of caseation.

No nodules were found in the cerebellum, pons, medulla, or spinal cord, all of which, to the naked eye at all events, appeared normal. On making sections of the brain, numerous small nodules, about the size of hemp-seeds, were found projecting into the lateral ventricles. These were hard and firm like the larger cortical nodules, and were not connected with the choroids (see Plate 4, Fig. 1).

The salient points in the case then are: an infant developed in an apparently normal fashion for a year; then took fits lasting for several hours, and thereafter remained in a semi-conscious condition for four weeks, dying of an intercurrent empyema. During the whole of her stay in hospital her appearance suggested cerebral mischief, but having departed from the diagnosis of meningitis we did not know what was the matter. We also wish to refer to the puzzling appearance of the lumbar puncture fluid. It was perfectly clear when first withdrawn, but, as it cooled, became opalescent from a precipitation in it of minute shreds of fibrin about  $\frac{1}{2}$  mm. long. We have never before seen anything precisely similar. It was equally unlike the coagulum which often

TABLE I. CASES OF TUBEROUS SCLEROSIS

No.	Reported by	Sex.	Age at, and Cause of Death.	Family History.	Initial Symptoms.	Convulsions.	Mental Condition.	Paralyses, &c.	Other Symptoms and Lesions.	Adenoma Subacuum.	Visceral Tumours.
1	Bourneville 1880	f.	15 Acute Epilepsy	Not neuropathic	Squint during 1st year	From 2nd year. In series. Major and minor attacks. Latterly every day. 340 on day of death.	Idiotic. Never spoke	Spastic. Bedridden	Sex development retarded	Present	Kidneys
2	Bourneville and Brissaud 1880	m.	4½ Heart failure	Neuropathic	Convulsions at 4th month	In series, about 20 per diem. Ceased latterly	Idiotic. Never spoke		Congenital heart disease		Thyroid Thymus
3	Bourneville and Bonnaire 1881	m.	5½ Acute Epilepsy	Neuropathic	Convulsions at 6th week	Seven or eight daily up to 15th month, then at intervals of a week	Idiotic		Asphyxia neonatorum	Present	Kidneys
4	Bourneville and Bonnaire 1881	m.	5 Menses	Not neuropathic	Convulsions at 7½ months	Daily, up to 15 per diem. Maximum interval, 8 days	Appeared normal until 5th month. Progressive deterioration. Idiotic			Absent	Kidneys
5	Brückner 1882	f.	22 Phthisis	Not neuropathic	Imbecile from birth	Fits at 9 years; then Jacksonian epilepsy. Fits recurred at long intervals from 20th year	Idiotic	Chorea-like movements	Acute mania at 19 years		Not examined
6	Pollik 1882	f.	7½ Cachexia	Neuropathic	Convulsions during first nine days	Epilepsy from 7th year	Imbecile	Atrophy of muscles of hands	Absence of corpus callosum		Not examined
7	Koeh 1887	m.	33 Epilepsy		Convulsions after birth	Every two or three months	Idiotic	Right hemiplegia due to for-eops injury			Not examined
8	Bordoz 1895	m.	4 Operation for hydrocephalus	Not neuropathic	Convulsions at 4th month	Four or five daily after second year. Latterly localized—head and eyes	Imbecile	Chorea-like movements	Hydromyelia		Not examined
9	Bourneville 1895	f.	10 Phthisis	Neuropathic	Abnormal at 3rd month	Daily from 8th month till 2nd year. Ceased at 3rd year	Idiotic	Slight contractures		Present	Absent
10	Sailer 1898	m.	15 Acute Epilepsy	Neuropathic	Normal for 10 months; then a convulsion	Epileptic	Idiotic			Absent	Kidneys Duo-donum Kidneys
11	Scarpattotti 1898	f.	24 Acute Illness			Convulsion at 3-4 years	Mentally deficient (domestic servant)		Dornoid (?) on left side of nose		Kidneys
12	Jürgens 1898	m.	17½ Convulsions	Not neuropathic	Fits at 3rd month	About once a week from 5th month. Also minor attacks	Apathetic				Heart Kidneys

13	Bourneville 1899	f.	Neuropathic	Normal for 6 months; then a convulsion	At irregular intervals. 90 during a year.	Imbecile. Learned to speak at 3rd year		Kidneys
14	Jacobaeus 1903	m.	Neuropathic	Imbecile from birth	About 16-20 per annum. Occur in pairs	Idiotic		Kidneys
15	Pallagatti 1904	m.	Neuropathic	Imbecile from birth	Epileptic	Idiotic		Present from early months
16	Campbell 1905	m.			About 5 fits in the month	Idiotic		Present
17	Perusini 1905	m.			10-12 daily	Idiotic	Bedridden. Contractions	Absent
18	Vogt 1909	m.	Not neuropathic	Convulsions at 6th month	Epileptic	Idiotic		Present
19	Vogt 1909	f.		Convulsion at 9th month	A few convulsions up to the 5th year.	Moderate degree of mental defect	Polynuria, dropsy, tumour-cells in urine	Present from 8th year
20	Vogt 1909	m.	Not neuropathic	Convulsions at 18th month	Three or four per month	Mentally defective		Present
21	Volland 1909	m.	Neuropathic	'Nervous' from birth	Began during dentition and became worse at 4th year. Also minor attacks	Imbecile. Spoke by 3rd year, but deteriorated later	Spastic	Present since early childhood
22	Volland 1909	m.	Neuropathic	Defective from birth. Convulsions at 4 years	86 severe and 50 mild in 1 year	Deteriorated greatly. Idiotic		Present at 11th year
23	Volland 1909	m.	Neuropathic	'Normal' during 1st year. Difficulty in learning to walk	From 3rd year; 2 or 3 at a time	Deteriorated. Idiotic	Spastic	
24	Vogt 1910	m.			From 2nd year	Idiotic		Present since childhood
25	Vogt 1910	m.			Epilepsy	Idiotic		Present
26	Vogt 1910	m.	Neuropathic	Mental defect	Epilepsy	Idiotic		
27	Bonfigli 1910	m.	Neuropathic	Convulsions since birth	8-10 daily	Idiotic	Spastic; athetosis	
28	Bonfigli 1910	m.		Convulsions in infancy	At intervals of 10-15 days	Idiotic		Left kidney
29	Fowler and Dickson 1910	f.		Developed normally until fit occurred at 1 year	One convulsion	Apathetic	Uræmia	Left kidney Heart



forms in the cerebro-spinal fluid from a case of tuberculous meningitis, and the turbidity produced by pus. There is no mention of the cerebro-spinal fluid in any recorded case of tuberous sclerosis.

On going through the literature one finds that more space is given to the pathology than to the symptoms of the disease. We have, however, found twenty-eight cases in which clinical notes are given, and although the details are in many cases meagre, we have made an analysis of the main clinical features. (See Table I.)

i. *Sex and Antecedent History.* Of the twenty-nine cases (including our own) nine were females and twenty males. As in other forms of imbecility a neuropathic heredity is common, being well marked in twelve out of twenty cases in which information is given. The average age of the fathers was 33; of the mothers, 27; the disease, therefore, does not tend to affect offspring of parents at the extremes of reproductive life. The position of the patient is stated in nine cases; in four it was the first child. Syphilis is so rare that it may be excluded as a cause.

ii. *Symptoms. Epilepsy and Mental Defect* are invariable. The convulsions, which were the first symptom that anything was wrong in fifteen cases, began during the first year in just over half the patients. There is nothing especially characteristic about the convulsions. The rule is that they occur in small series at intervals of a few weeks. They are usually general; one case had also Jacksonian epilepsy, and a few, minor as well as major seizures. Sometimes the epilepsy becomes worse with lapse of time, and culminates in an acute attack—the status epilepticus. One patient had only a single fit in the whole course of her life, but she is an exception in this respect.

Most patients are low grade imbeciles, able to articulate a few words at most, and inattentive to their surroundings. In only two cases is the mental defect described as moderate. Some of the patients seem to have been absolutely normal before the first convulsion occurred, and even when due allowance is made for the manner in which parents shut their eyes to evidences of mental defect, we think that, as in our case, in which the question was carefully gone into, patients with tuberous sclerosis *may* develop normally for the first year or so. When once epilepsy sets in development is checked; speech, if it has been acquired, is arrested, and the mental condition deteriorates. In nine cases some abnormality was noticed before the fits occurred—nervousness, squinting, backwardness.

Considering how extensively the cortex is diseased, it is rather remarkable that contractures and spastic paralysis are uncommon—six cases only—and that tremor is not recorded in this series. As in congenital imbecility generally, other malformations are not very rare. Congenital heart disease, spina bifida, hydromyelia, and absence of the corpus callosum have been noticed.

iii. *Associated Tumours.* The most interesting feature of the condition is the frequency with which tumours of the kidneys, heart, skin, and other

organs coexist with the cerebral sclerosis. (See Table II). In only six of these twenty-nine cases did the tuberous sclerosis exist alone, and in some of these, probably, the nervous system only was examined.

*Renal Tumours* are found in nineteen of the twenty-nine cases, and in some of the negative cases the abdominal viscera were not examined. In all but three cases both kidneys were affected. The renal tumours are somewhat vaguely described, and it is difficult to understand their nature. They are usually small, multiple, and not infrequently undergo cystic degeneration. They have generally been called adeno-sarcomata, or simply 'cancerous'. Vogt calls them lipo-sarcomata; others regard them as myomatous.

*Tumour of the Heart* occurs in only three cases in this series. This number, however, does not give a true idea of the frequency of the tumour, because most patients with this lesion die in infancy, and have been recorded as cases of congenital tumour of the heart. In a number of them the brain has either not been examined, or the association of cerebral sclerosis has been looked on as merely fortuitous. One patient in this series with a heart tumour reached his twenty-fourth year, but this is exceptional; the others died in infancy.

Tumours of the *thyroid, thymus, breast, and duodenum* are also recorded.

*Adenoma Sebaceum.* It is stated that those who suffer from this affection of the skin are nearly always of low intelligence; it is not uncommon in institutions for the feeble-minded. It is a developmental anomaly, but it is not usually present at birth, though it may appear during the first six months. It consists of numerous small, closely-set tumours symmetrically disposed on the face, chiefly about the sides and bridge of the nose, naso-labial folds, chin, and forehead. It gives rise to no symptoms. Similar tumours are sometimes found on the skin of the trunk. The histology of the condition is not absolutely settled, but most writers describe the tumours as masses of sebaceous glands embedded in a more or less vascular matrix—sebaceous naevus.

Adenoma sebaceum was present in thirteen of these twenty-nine cases. The date of its first appearance is given in four—in the first month of life, from early infancy, since childhood, and from the eighth year.

TABLE II.

DISTRIBUTION OF LESIONS IN TWENTY-NINE CASES OF TUBEROUS SCLEROSIS.

Tuberous Sclerosis	.	.	.	.	.	.	.	.	6
"	"	Adenoma Sebaceum	.	.	.	.	.	.	2
"	"	"	"	Renal Tumour	.	.	.	.	9
"	"	"	"	Rhabdomyoma	.	.	.	.	1
"	"	"	"	Thyroid Tumour	.	.	.	.	1
"	"	Renal Tumour	.	.	.	.	.	.	6
"	"	"	"	Rhabdomyoma	.	.	.	.	1
"	"	"	"	Duodenal Tumour	.	.	.	.	1
"	"	Thyroid Tumour	.	.	.	.	.	.	1
"	"	Rhabdomyoma	.	.	.	.	.	.	1
									29

### *Microscopical Examination.*

*Brain, Cortical Nodules.* Sections were made of several of the cortical nodules, and the appearances were found to be similar in all. Under a low

power, the nodules show a much more homogeneous and much denser structure than the neighbouring grey and white matter. Nerve cells are much less numerous, and vessels are scanty, and the transition between nodule and surrounding brain tissue is more definitely marked near the surface than towards the deeper parts. In the former position, the complete transition may be followed practically within the limit of one field under a magnifying power of, say, 100 diameters, as may be seen in Plate 5, Fig. 5.

The increased density of the tissue is seen to be due to the closely woven network of proliferated neuroglial fibrils, the density of these being most marked towards the central parts of the nodules, and also, but not quite to so extreme a degree, at and immediately beneath the free surface.

Under an ordinary low power, e.g. as seen in Plate 5, Fig. 2, one of the most noticeable features is the presence of numerous groups of large irregularly shaped cells, mostly situated immediately beneath the denser surface layer of proliferated glia, and also in the more peripheral lateral parts of the nodule. In the denser central part, they are somewhat smaller in size and much scantier in numbers, being scattered singly rather than in groups. There seem to be little doubt that these are large ganglionic nerve-cells—not neuroglia cells—in their nature, both from the character of their nuclei and from the fact that nerve fibres could be traced into their processes. An unusual feature, however, was the fact that they not uncommonly possessed two and even three nuclei, a character which at first inclined one to suspect that they might possibly be enlarged glial cells. As may be seen from Plate 6, Figs. 2 and 3, degenerative changes are well advanced in some of these cells. The nucleus is often eccentric, and may show karyolysis or may be absent altogether; and the body of the cell may become invaded with small mononuclear phagocytic cells (Plate 6, Fig. 3), and undergo disintegration. These peculiar groups of large ganglionic cells are not found in the neighbouring unaffected brain tissue, where the cortical cells are still arranged in their normal layers, though many of them show well-marked degenerative changes—due no doubt to the terminal acute disease (empyema, &c.). In no case, however, was this degeneration in the cells of the normal convolutions so extreme as in the tuberous nodules. Where the nodules extend into the white matter, the large ganglionic cells are also present.

*Ventricular Nodules.* These are quite distinct from the cortical nodules in their characters, and seem to be of the nature of so-called ependymal granulations. They consist of proliferated glial cells and fibres, and frequently show irregular points and lines of calcification, sometimes along capillaries, sometimes apparently independent of these. No giant nerve cells were found in any of them, nor could anything resembling the peculiar 'gland-like' structures described by Campbell be discovered.

*Rhabdomyomata in Heart.* Microscopical examination of the small nodules from the right auricular appendix showed them to be rhabdomyomata, conforming to the classical descriptions of these extremely rare tumours. As we propose to give a more detailed description of these elsewhere, we shall only

summarize the appearances here. They consisted of large, loosely arranged, extremely irregular and highly vacuolated cells, containing irregularly striated fibres, some in bands or bundles, but many running singly and forming a loose interlacing 'tumultuous' network, in the meshes of which were large vacuole-like spaces (see Plate 6, Figs. 4 and 5). Most of the cells contained a single bladder-like nucleus, with distinct outline, and poor in chromatin. Many, however, showed two or more—even as many as half a dozen—nuclei. The nodules were comparatively non-vascular, and contained very little connective tissue, the framework of the tumours consisting mainly of striated muscular fibres derived from the cells. The surrounding heart muscle showed considerable increase of fibrous connective tissue, which formed a well-marked capsule around the tumours.

The other organs, e.g. the liver, kidneys, &c., showed merely general toxic changes, such as cloudy swelling, &c., presumably accounted for by the presence of empyema and broncho-pneumonia. No tumours were found in any of the organs except the brain and heart, as above described.

There can be little doubt that the cardiac, renal, and cutaneous lesions are of the nature of true neoplasms, and it therefore only remains to discuss the nature of the nodules in the brain. The earlier observers were of opinion that these were probably of chronic inflammatory origin, but this is not borne out by the histological findings. The pia is thin and non-adherent over the affected areas, and the peculiar groups of large nerve-cells incline us to the view that the condition is, like the lesions in the other organs characteristic of the condition, a neoplastic formation due to a developmental intermingling of ganglionic cells 'dislocated' from their proper environment, with consequent overgrowth of neuroglia in the affected areas.

As the actual aetiology of the condition, as far as it is at present understood, has been very fully discussed in recent papers by Campbell, Jacobaeus, Sailer, Vogt, Wolbach, and others, and as we have nothing further to add in possible explanation of the causation of the condition, we are content simply to draw attention, as the other writers have done, to the remarkable combination, characteristic of this disease, of *congenital tumours in the brain, heart, kidneys, skin, and, less commonly, in certain other organs*. As to what the exciting cause of these tumours is, we can only assume that they are produced by a developmental intermingling of the growing tissues, such as may cause certain adrenal, parotid, testicular, and other forms of congenital neoplasms. Further than this statement our knowledge of the causes of tumour growth does not at present carry us.

#### *Duration of Life and Cause of Death.*

Eight of the patients died by the fifth year, and twenty by the sixteenth. One patient lived to thirty-five. She had only a few fits between the age of nine months and five years, and was moderately intelligent, but was a typical

case with nodular sclerosis, adenoma sebaceum, and renal tumour. Death was due to kidney tumour.

Death was directly due to epilepsy in nine cases, to renal tumour in two—perhaps three—and to other, accidental, causes in the remainder.

### *Diagnosis.*

The possibility of diagnosing the disease from other forms of epileptic imbecility depends on detecting some of the associated tumours. Adenoma sebaceum is the most obvious of these. Some of the tumours of the kidneys appear to have been large enough to be detected by palpation, and twice at least they have actually been recognized by the occurrence of renal symptoms and the presence of tumour cells in the urine. It is only within the last year or two, however, that any attempt has been made to arrive at a clinical diagnosis.

The main features of the cases recorded clinically as well as pathologically are set down in Table I. A number of other cases have also been reported without clinical histories; these have not been included in the Table.

### *Conclusions.*

(i) Tuberous sclerosis constitutes a definite form of idiocy. It may be diagnosed during life by the recognition of some of the associated tumours in a mentally defective person who is, or has been, subject to epileptiform convulsions.

(ii) The condition is characterized by the presence of congenital 'dislocation' tumours in all or any of the following sites:—brain, kidney, heart, skin,—more rarely, pancreas, duodenum, thyroid, breast.

(iii) The condition in the brain is established probably at, or soon after, the seventh month of foetal life.

(iv) The pathogenesis of the condition is still entirely unknown.

### REFERENCES.<sup>1</sup>

1. Berdez, *Ziegler's Beitr. z. path. Anat. u. z. allg. Path.*, 1895, xvii. 648.
2. Bonfigli, *Monatsehr. f. Psychiat. u. Neurol.*, 1910.
3. Bonome, *Atti r. Inst. Veneto di sci., lett. ed arti*, 1902-3, lxii. 206.
4. Bourneville, *Archives de Neurol.*, Paris, 1880-1, i. 69.
5. Bourneville, *Progrès méd.*, Paris, 1896, 129; and 1899, 241.
6. Bourneville et Bonnaire, *Progrès méd.*, Paris, 1881, 1007; and *Bull. de la soc. d'anat. de Paris*, 1881, lvi. 180 and 545.
7. Bourneville et Brissaud, *Archives de Neurol.*, Paris, 1880-1, i. 397.
8. Brückner, *Archiv f. Psychiat.*, Berlin, 1882, xii. 550.
9. Campbell, *Brain*, Lond., 1905, xxviii. 367.
10. Finlay, *Rev. of Neurol. and Psychiat.*, Edin., 1905, iii. 391; *Journ. of Pathol. and Bacteriol.*, 1905, x. 397.
11. Hartdegen, *Archiv f. Psychiat.*, Berlin, 1881, xi. 117.
12. Jacobaeus, *Nordisk medicinskt Archiv*, Stockholm, 1903, xxxvi. 1.

<sup>1</sup> No attempt has been made to give the full literature here. A very complete list will be found in Vogt's papers, especially in that published in the *Monatschrift für Psychiatrie und Neurologie*, 1903, Bd. 24, p. 147.

13. Jürgens, *Berl. klin. Wochenschr.*, 1898, xxxv. 302.
14. Koch, *Neurolog. Centralbl.*, 1887, vi. 49.
15. Neurath, *Arbeiten aus Prof. Obersteiner's Labor.*, 1899, vi. 131; and *ibid.*, 1908, xiv. Sep.-Abdr.
16. Pelagatti, *Annales de dermatol.*, 1904, v. 983, 989.
17. Pelizzi, *Annali di freniatria e scienze affini del Manic. di Torini*, 1901 (quoted by Vogt).
18. Perusini, *Monatschr. f. Psychiat. u. Neurol.*, 1905, xvii. 169.
19. Pollák, *Archiv für Psychiat.*, 1882, xii. 157.
20. Ponfick, *Verhandl. d. deutsch. pathol. Gesellsch.*, Berlin, 1902, iv. 226.
21. Pozzi, *L'Encéphale*, 1883, 210 (quoted by Vogt).
22. v. Recklinghausen, *Verhandl. d. Berliner geburtshülflichen Gesellsch.*, 1863, Heft 14, 73; and *Monatschr. für Geburtskunde*, 1864, xx. 1.
23. Rothe, *Allgem. med. Centralztg.*, Berlin, 1901, lxx. 175.
24. Sailer, *Journ. Nerv. and Ment. Dis.*, New York, 1898, xxv. 402.
25. v. Scarpatetti, *Archiv für Psychiat.*, 1898, xxx. 537.
26. Simon, *Virchow's Archiv f. pathol. Anat. u. Physiol.*, Berlin, 1873, lviii. 310; and *Revue mensuelle des maladies de l'enfance*, 1883, 555.
27. Tedeschi, *Rivista sperimentale di freniatria e di med. legale*, 1884, xx. 153; and *Ziegler's Beitr. z. path. Anat. u. z. allg. Path.*, 1897, xxi. 43.
28. Thibal, *Thèse de Paris*, 1888.
29. Vogt, *Münch. med. Woch.*, 1908, lvii. 2037; *Zeitschrift für die Erforschung und Behandlung des jugendlichen Schwachsinn*, 1908-9, ii. 1, and other papers; *Die Epilepsie im Kindesalter*, Berlin, 1910, *passim*.
30. Volland, *Zeitschr. f. d. Erforschung und Behandlung des jugendlichen Schwachsinn*, 1909, iii. Heft 3.
31. Wolbach, *Journ. Med. Research*, 1907, xvi. 496.

## DESCRIPTION OF PLATES.

PLATE 4, FIG. 1. Photograph of the brain, showing the nodules of tuberous sclerosis, both in surface view and on section. The position of the nodules, both cortical and ventricular, can be made out by referring to the blackened areas in Fig. 2. The general outline of the convolutions is but little altered, a fact of some importance in considering the time of onset of the condition (see conclusion No. iii).

PLATE 4, FIG. 2. Outline diagram of the same, showing the nodules marked in black.

PLATE 5, FIGS. 1 and 3. Microscopical sections of a neighbouring unaffected convolution, the former at surface, the latter at deeper part of cortex, for comparison with Figs. 2 and 4, which are taken from corresponding positions in one of the cortical nodules.  $\times 100$  diam.

PLATE 5, FIG. 2. Section towards surface of a cortical nodule of tuberous sclerosis, showing glial overgrowth and groups of large ganglionic cells. Compare with Fig. 1.  $\times 100$  diam.

PLATE 5, FIG. 4. Section towards centre of nodule, showing density of glia and diminution in number of nerve cells. Compare with Fig. 3.  $\times 100$  diam.

PLATE 5, FIG. 5. Section through edge of nodule (upper left portion) and adjoining cortex (lower right portion) near surface of brain.  $\times 100$  diam.

PLATE 6, FIGS. 1, 2, and 3. Groups of 'giant' ganglionic nerve cells found in the nodules. These show various degenerative changes, e.g. displacement and disappearance of nucleus, invasion by phagocytic cells (Fig. 3), &c.  $\times 450$ ,  $450$ , and  $300$ .

PLATE 5, FIGS. 4 and 5. Sections of rhabdomyoma of heart.

Fig. 4 shows low-power view of edge of tumour (lower right portion), the upper left portion consisting of proliferated fibrous tissue and atrophied heart muscle.  $\times 45$ .

Fig. 5 shows the structure of the tumour under a higher power. Note the 'tumultuous' arrangement of the striated muscle fibres, and the extraordinary vacuolation of the cells. There is very little connective tissue present, practically all the fibres shown in the photograph consisting of striped muscle.  $\times 450$  diam.

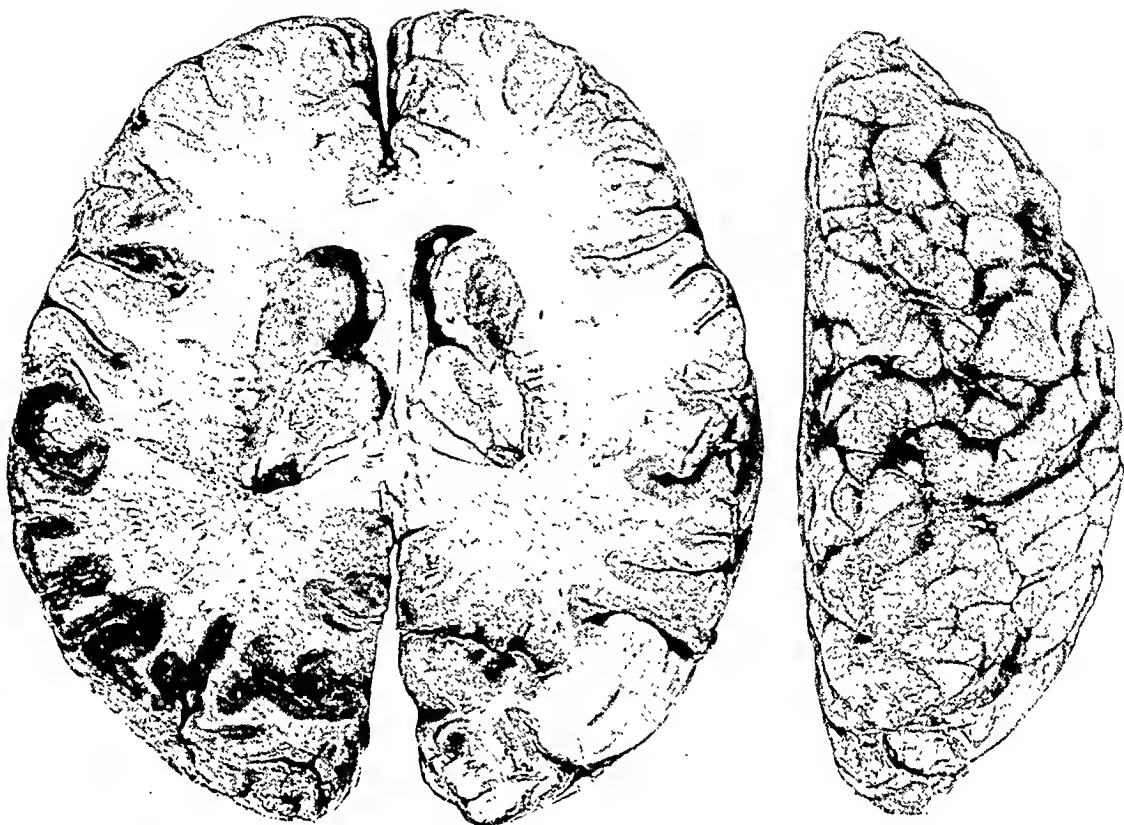


FIG. 1



FIG. 2





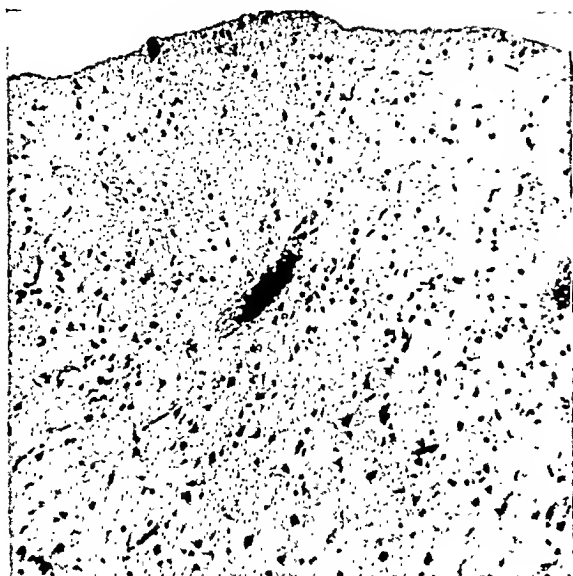


FIG. 1  $\times 100$

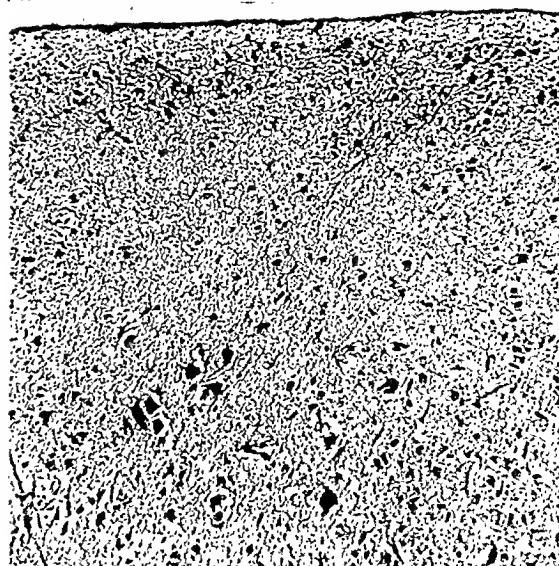


FIG. 2  $\times 100$

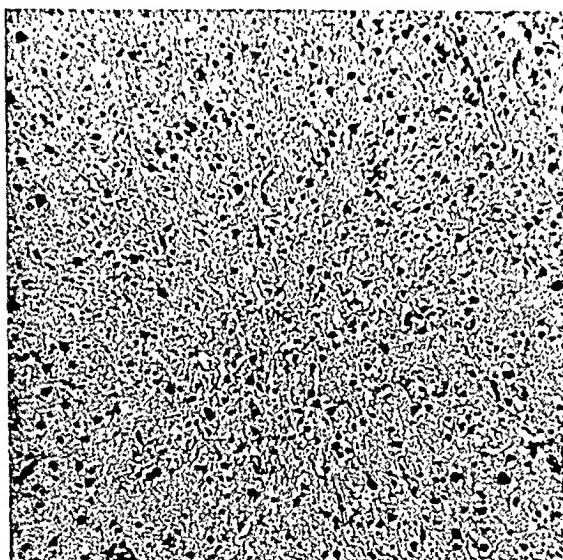


FIG. 3  $\times 100$

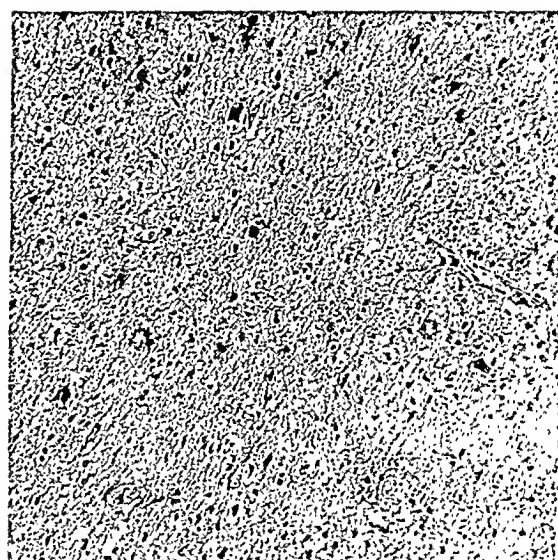


FIG. 4  $\times 100$

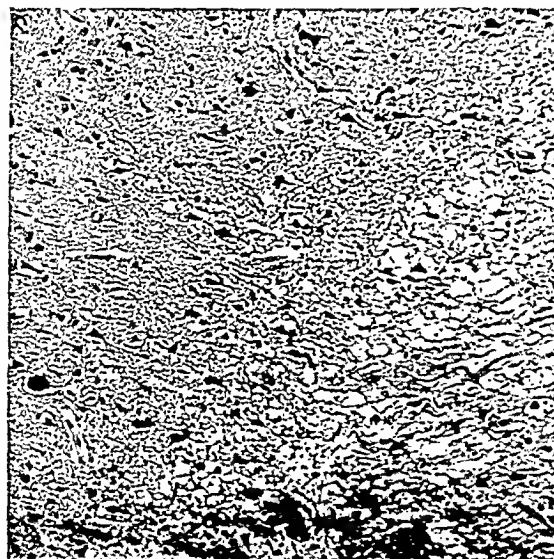


FIG. 5  $\times 100$



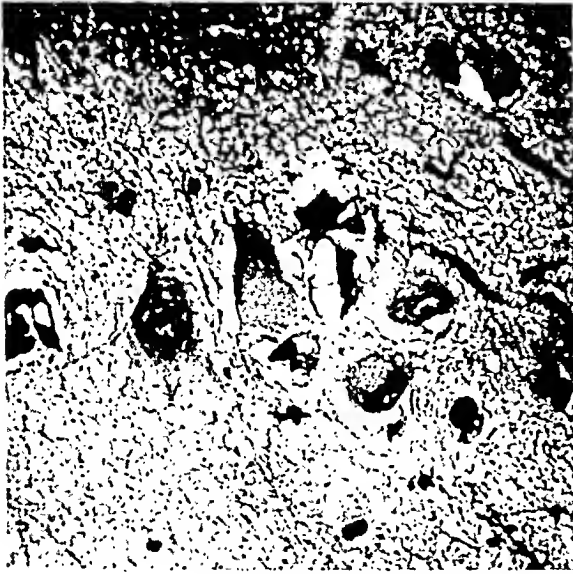


FIG. 1  $\times 450$

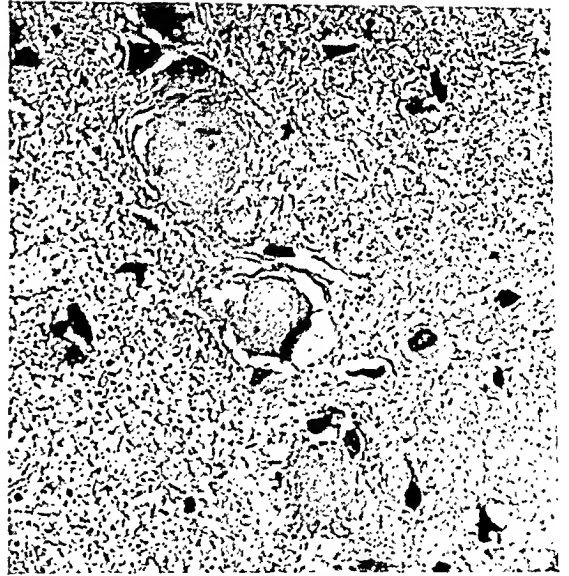


FIG. 2  $\times 450$

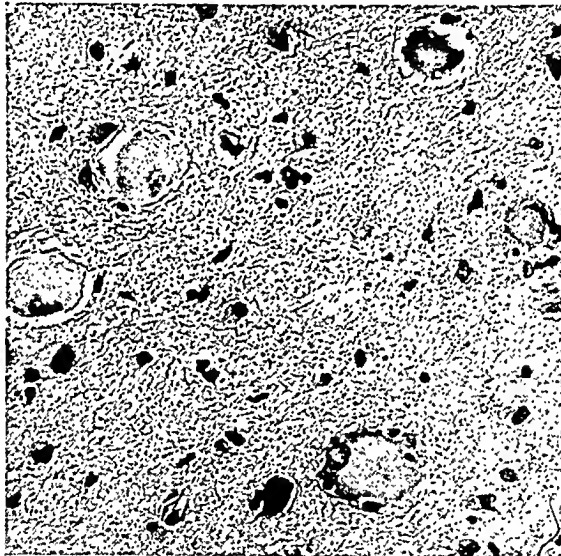


FIG. 3  $\times 300$

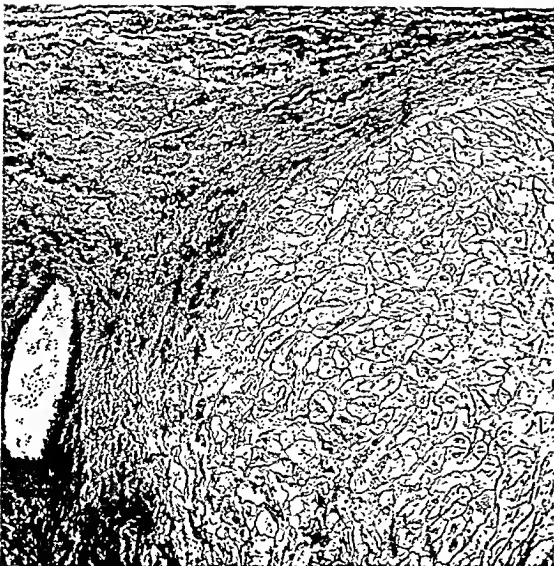


FIG. 4  $\times 45$



FIG. 5  $\times 450$



# COUPLED RHYTHMS OF THE HEART

By JOHN COWAN AND W. T. RITCHIE

With Plates 7-18

## INDEX.

	PAGE		PAGE
I. INTRODUCTION.—The Interpretation of Graphic Records of the Contractions of the Heart . . . . .	55	stimuli from the same part of the heart . . . . .	71
II. DEFINITION OF COUPLED RHYTHM . . . . .	58	V. CHIEF CLINICAL FEATURES OF THE CASES RECORDED . . . . .	72
III. COUPLED RHYTHMS OF THE VENTRICLES—		VI. EXPLANATION OF COUPLED RHYTHMS—	
i. In Partial Auriculo-Ventricular Heart-block . . . . .	59	Synchronous Contraction of Auricle and Ventricle followed by an Extra-systole . . . . .	77
ii. In Complete Auriculo-Ventricular Heart-block . . . . .	60	Synchronous contraction of Auricle and Ventricle associated with a Coupled Rhythm . . . . .	78
iii. In Perpetual Arrhythmia of the Ventricles . . . . .	61	The relation between Coupled Rhythms and Respiration . . . . .	79
iv. In which a Ventricular Extra-systole recurs after each Physiological Beat . . . . .	63	Undue Prolongation of Diastole causing a single Extra-systole . . . . .	80
IV. COUPLED RHYTHMS OF AURICLES AND VENTRICLES—		Undue Prolongation of Diastole producing regularly recurring Extra-systoles . . . . .	81
i. In which the beats are due to stimuli from different parts of the heart . . . . .	67	Coupled Rhythm in Perpetual Arrhythmia . . . . .	82
ii. In which both beats are due to			

## I. Introduction.

THE clinical observations upon certain forms of cardiac arrhythmia, which we now record, are founded mainly upon a study of simultaneous graphic records of the cardiac impulse and of the pulsations in the arteries and the jugular veins, according to the methods introduced by Mackenzie. Some of our records were obtained by means of Mackenzie's polygraph, others by the Knoll-Hering polygraph, and others again by a polygraph recently designed by one of us.

We are aware that all deductions regarding the time, duration, and sequence of contraction of the chambers of the heart that may be drawn from graphic records obtained by mechanical methods of registration lack the precision and accuracy of the evidence obtainable by means of the string galvanometer. The inertia of the recording apparatus in ordinary clinical use is a possible source of fallacy which is too often disregarded. The slow rate at which

the recording surface travels, and the inaccuracy or absence of the time-marker, render the finer analysis of many tracings recorded in the literature more or less inexact and unsatisfactory, and thus may vitiate the deductions that are drawn therefrom. Notwithstanding these sources of error, however, mechanical methods of recording the movements of the heart yield much information which is not obtainable by other clinical methods.

In jugulo-carotid tracings the six main positive waves which may appear are the auricular wave,  $a$ ; the early ventriculo-systolic wave,  $b$ , transmitted to the veins from the ventricle (Fredericq(15), Bard(3), Piersol(61), Bachman(1)); the carotid elevation,  $c$ ; the late ventriculo-systolic wave,  $v^1$ ; the early ventriculo-diastolic wave,  $v^2$  (which terminates when the tricuspid valves open); and the  $h$  wave (the  $b$  wave of A. G. Gibson (19)), which both Gibson and Hirschfelder (30) attribute to the temporary closure of the tricuspid valves by the inrush of blood from auricle to ventricle. When the waves  $v^1$  and  $v^2$  in our tracings are fused together so that the notch marking the end of  $v^1$  and the start of  $v^2$  is indefinite, the compound wave is designated simply  $v$ .

If we desire to ascertain by means of the polygraph the precise time, duration, and sequence of contraction of the chambers of the heart in cases of cardiac arrhythmia, simultaneous tracings from the jugular vein and from an artery are insufficient and are liable to lead to error. The phlebogram and sphygmogram afford only an approximate, not an exact, standard for determining the commencement and termination of ventricular systole. Moreover, the duration of the presphygmic period is too variable, and our knowledge regarding the rate of transmission of the pulse wave from the aortic orifice to the subclavian or carotid artery in the human subject is too uncertain, to permit of any reliable inference being drawn from the  $a$ - $c$  interval in regard to the  $As$ - $Vs$  interval.

In the cases which we record, the commencement and termination of auricular systole were usually estimated from the start and the apex respectively of the auricular wave in the jugulo-carotid tracing. The auricular wave is usually more constant and better defined in the jugulo-carotid tracing than in the cardiogram. If an auricular wave be present in the cardiogram, it is, in our experience, usually positive and single. More rarely it is a negative wave due to the upward pull upon the ventricle during auricular systole, as was first demonstrated by Wenckebach (83). The commencement of the auricular wave in the jugulo-carotid tracing must be slightly later than the commencement of auricular systole, and the delay may presumably vary somewhat according to the degree of congestion within the superior vena cava and jugular vein. The commencement of the positive auricular wave in the cardiogram must be likewise slightly later than the commencement of auricular systole. But in either case the error is probably slight. Further, although experimental curves seem to indicate that auricular contraction persists well into the period of ventricular contraction, the apex of the auricular wave in the jugulo-carotid tracing probably indicates the termination of 'effective' auricular

systole, and it has been so regarded in our analysis of tracings. If the heart's rate be frequent the  $\alpha$  wave may be mingled with the  $h$  wave, or even with the  $v^2$  wave if the rate be still more rapid.

Whenever a satisfactory cardiogram could be obtained, the commencement of ventricular systole was estimated from the beginning of the abrupt ventriculo-systolic rise on the cardiogram. We seldom find that this abrupt rise is preceded by the  $I$  wave described by Robinson and Draper. The end of ventricular systole was regarded as coinciding with the termination of the systolic plateau on the cardiogram. The termination of the  $v^2$  wave in the jugulo-carotid tracing was considered as indicating the moment at which the tricuspid valves opened. It is usually almost synchronous with the commencement of the ventriculo-diastolic rise on the cardiogram.

The commencement and duration of ventricular diastole should likewise be estimated from the cardiogram and not from the sphygmogram. This is particularly important when determining the duration of a post-extra-systolic pause, for ventricular contraction does not usually last so long in an extra-systole as in the antecedent physiological beats (see Figs. 8, 10, 13, and 17). And, as the  $Vs-c$  interval is longer after an extra-systole than after a normal beat, if the duration of systole be judged from the sphygmogram, the post-extra-systolic pause will probably be wrongly estimated.

Except in cases in which it was impossible to obtain a satisfactory cardiogram on account of the thickness of the chest wall or of the voluminous state of the lungs, the  $As-Vs$  interval was estimated by measuring the interval between the commencement of the  $\alpha$  wave in the jugulo-carotid tracing and the start of the ventriculo-systolic rise on the cardiogram ( $\alpha-Vs$  interval). As already stated, this is, in our opinion, more reliable than the  $\alpha-c$  interval as an index of the  $As-Vs$  interval.

In graphic records from cases in which there was no cardiac arrhythmia, we find that the average duration of the  $\alpha-Vs$  interval is 0.120 of a second, the shortest interval being 0.05 second, with a pulse rate of 95.2 per minute. The average  $Vs-c$  interval is 0.066 of a second, the longest being 0.11, and the shortest being 0.03 of a second. These figures are in substantial agreement with those given by Robinson and Draper, the shortest  $Vs-c$  interval in their series of cases being 0.038 and the longest being 0.177 of a second, and also with those given by Rehfish, who estimates the  $Vs-c$  interval at 0.07 of a second. The average  $c$ -brachial interval in our series of cases without arrhythmia is 0.065 of a second, the shortest being 0.04 and the longest 0.08 of a second. The average duration of ventricular systole is 0.326 of a second, the shortest being 0.28, and the longest 0.46 of a second. These figures indicate that the commencement, duration, and termination of ventricular systole cannot be estimated accurately from a study of jugulo-carotid and brachial or radial tracings.

In the tracings which illustrate this paper, 1 indicates the commencement of the  $\alpha$  wave; 2 the beginning of ventricular systole as determined in the



cardiogram; 3 the appearance of the carotid elevation in the phlebogram; 4 the brachial (or radial) wave in the sphygmogram; 5 the termination of ventricular systole; and 6 the opening of the auriculo-ventricular valves.

## II. *Definition of Coupled Rhythm.*

Much speculation and controversy have gathered around those forms of cardiac arrhythmia in which two beats of the heart are separated from each other by a short diastolic pause, while the second beat of each couple is followed by a long diastolic pause before the first beat of the next couple occurs. Such an allorhythmia, or regularly recurring arrhythmia, we designate a coupled rhythm of the heart rather than a *pulsus bigeminus*, because the two beats of each couple are not necessarily so identical in nature as to justify us in regarding them as 'twin beats'. Coupled rhythms of the heart have also been described under the terms 'hemisystole' (von Leyden, Schatilloff), 'systolia alternans' (Unverricht), 'bigeminy' (Riegel), 'pulsus pseudoalternans', and 'continuous bigeminus'. The condition has also been designated 'pulsus coturnisans' ('le pouls coturnisant') because the rhythm of the sounds of the heart resembles the cry of the quail (*coturnix*), which, according to Merklen, the French peasants imitate by saying 'Paye tes dettes'.

Under the term coupled rhythms of the heart, we do not include the disturbance of the heart's action occasioned by a single extra-systole occurring at irregular intervals in an otherwise rhythmically beating heart. Nor do we include the *pulsus alternans*, for although in *pulsus alternans* every alternate beat of the ventricles is feebler, and every alternate pulse wave is of smaller volume than that which precedes and that which follows it, the rhythm of the heart's contraction remains perfectly regular, as has been demonstrated by Volhard, Rihl, and others. The alternating pulse, which is undoubtedly evidence of grave cardiac enfeeblement, is usually regarded as indicating exhaustion of contractility of the heart. In the experiments of Trendelenburg and Hering (28), the feebler beat was demonstrated to be due to partial hyposystole or asystole, namely to enfeeblement or failure of a portion of the ventricular musculature, rather than to a weak contraction of all the ventricular muscle fibres. In the alternating pulse the smaller and larger beats of the arterial pulse may be apparently rhythmic (Fig. 1), or the smaller beat may be delayed appreciably (Fig. 2). The delay of the smaller pulse wave, which has been recognized ever since Traube recorded his classical observations, is the result, as shown by Hering (26) and Volhard, of a longer presphygmie period associated with the feebler ventricular contraction. In pure *pulsus alternans*, however, the smaller arterial pulse wave is never premature, whereas in the forms of arrhythmia which we term coupled rhythms the diastolic pause after the second or smaller beat is always longer than that between the first and second beats of each pair. The difference between the sphygmographic tracings of coupled rhythms and *pulsus alternans* was clearly demonstrated by Volhard, who pointed out that owing to the delay of the smaller pulse wave the regularity of true alternation

is obscured and arrhythmia is simulated, whereas in a coupled rhythm the irregularity tends to be obscured and regularity to be simulated.

From an analysis of the cases of coupled rhythm of the heart which have come under our observation and of cases which are recorded in the literature, we find that coupled rhythm is not an entity, but that coupled rhythms are of many forms and arise in many different ways. Discussing the *pulsus bigeminus* Wenckebach (80) concludes that although the two beats of each couple may be of identical nature, and that consequently there is a true bigeminy of the heart, this condition may be closely simulated if an extra-systole recurs regularly after each normal beat, or if a ventricular beat be missed regularly owing to failure of conductivity in the auriculo-ventricular bundle.

It is convenient to divide coupled rhythms of the heart into two groups: (1) those of the ventricles alone; and (2) those in which both auricles and ventricles participate in the coupling.

### III. *Coupled Rhythms of the Ventricles.*

i. *In partial auriculo-ventricular heart-block.* Coupled beats of the ventricles are occasionally met with in cases presenting a delay in the conduction of stimuli to the ventricles. This form of coupled rhythm is shown in Fig. 3. The tracings were obtained from a girl (Case I), aged seventeen, who was suffering from acute rheumatism. On her admission to hospital the pulse was notably irregular, the intervals between the beats being long and unequal. The irregularity of the pulse continued for several days, and defective conductivity persisted for several weeks after the pulse had become regular.

The irregular rhythm was at first very erratic, the beats appearing as a rule in twos and threes, with a long pause between each group. Occasionally there was a 2 : 1 rhythm, or a group of four ventricular beats, but there was no constancy in the arrangement. In Fig. 3 an apparent series of five coupled beats is seen, but the fourth pair are really the second and third beats of a group of three, the first of which produced the ordinates when the clock-work of the polygraph was momentarily stopped. The jugulo-carotid tracing is somewhat difficult to interpret because the defective conductivity led to the occasional conjunction of *v* and *a* waves. But the series of tracings obtained on successive days from this patient and recorded in an earlier number of this Journal (7) is, we think, sufficient evidence that our interpretation of Fig. 3 is correct.

The *a-c* interval is always unduly prolonged, as is shown in the diagram of Fig. 3. Whereas the *a-c* interval in our tracings from persons without cardiac arrhythmia is usually about 0.15 to 0.17 of a second in duration, the first auricular wave in Fig. 3 is not followed by a carotid wave until after an interval of 0.3 of a second. The second *a-c* interval measures 0.35 of a second, and thereafter the interference with conduction is so great that with the third auricular contraction the stimulus fails to pass to the ventricles and consequently the latter do not contract. During the long period of rest which the

auriculo-ventricular bundle thus obtains before the fourth auricular contraction occurs, the conductivity of the bundle again becomes so far restored that with the fourth auricular systole the stimulus is transmitted to the ventricles, and they respond by contracting. But even after the long period of rest the conductivity of the bundle was not fully restored, as is indicated by the  $a-c$  interval lasting 0.3 of a second. With the next beat conductivity becomes still further impaired, for the  $a-c$  interval is now 0.4 of a second. The sixth auricular contraction, like the third, evokes no ventricular response. Thus while the auricular rhythm is fairly regular, the coupled rhythm of the ventricles is due to partial auriculo-ventricular heart-block.

Cases of this form of coupled rhythm of the ventricles have been recorded by Mackenzie (48, 55), Joachim, Wenckebach (84), and Wardrop Griffith and Cohn.

ii. *Coupled rhythm of the ventricles in complete auriculo-ventricular heart-block.* When there is a lesion completely severing the auriculo-ventricular bundle, there is complete dissociation of the ventricular rhythm from that of the auricles. The auricles usually beat rhythmically about sixty to eighty times per minute, whereas the ventricular rate is fairly constant at about thirty to thirty-six beats per minute and the ventricular rhythm is regular. In some cases of auriculo-ventricular heart-block, however, an occasional extra-systole of the ventricles may be observed. In the case of partial auriculo-ventricular heart-block recorded by Wardrop Griffith and Cohn single ventricular extra-systoles were present. They are more often noticed, however, in complete auriculo-ventricular heart-block, the extra-systole being either interpolated, or being followed by a diastolic pause equal to that obtaining after the rhythmic ventricular systoles. Examples of such extra-systoles have been recorded elsewhere by one of us (68, 21). But as was pointed out by Goteling Vinnis and by Wenckebach (82), in some cases of complete auriculo-ventricular heart-block every contraction of the ventricles is followed after a constant interval by a second ventricular contraction, and this, in turn, by a long diastolic pause of the same duration as that which followed systole when the ventricles beat rhythmically. Wenckebach (80) records five cases presenting this form of coupled rhythm of the ventricles. Similar cases have been reported by Hering (26) (Case II of his series), Finkelnburg, and Hay (22).

No case has come under our observation in which the ventricular beats in complete auriculo-ventricular heart-block were constantly coupled. In one of our cases, however, the ventricular beats were, at one time, often although not constantly coupled. This coupling is shown in Fig. 25, taken from a man (Case II), aged 60, who had presented auriculo-ventricular heart-block for five years before the tracing in Fig. 25 was taken. We do not propose to dwell in detail upon the clinical features of this case. Tracings taken in 1905 have been recorded elsewhere (67), and certain features will be described more fully by one of us in conjunction with Dr. Jolly (34). One fact, however, to which we would draw attention is that the auricles are beating at a rate of from 250 to 300 per

minute (see Fig. 6). Electro-cardiograms demonstrate that the auricular contractions are co-ordinate beats, representing a condition which may be termed 'flutter' rather than 'fibrillation'.

In this patient, after the auriculo-ventricular block had persisted for at least five years, and after the auricular flutter had been present for many months, the ventricular rate, which had been constant at about 32 to 36 per minute, increased to 51 to 63 per minute. This increased frequency of the ventricles was associated with a well-marked group-beating of the ventricles. There were groups of from five to eleven, and in one instance sixteen, rapid ventricular beats (see Figs. 5 and 6), each group terminating with a long diastolic pause of about the same duration as that after a systole when the ventricles were beating rhythmically and less frequently. The following figures, taken from graphic records, represent the ventricular periods in seconds and show the group-beating:—

1.80, 1.00, 0.90, 0.94, 0.86, 0.92, 0.90, 0.976, 0.92, 0.90, 1.76, 1.00, 0.90 (Fig. 6)  
 1.68, 1.40, 1.00, 0.88, 0.90, 0.92, 0.88, 0.92, 0.92, 0.92, 0.90 . . . . .  
 1.76, 1.44, 1.00, 0.92, 0.96, 0.90, 0.95, 0.90, 0.93, 0.96, 0.95, 1.72  
 1.76, 1.44, 0.96, 0.95, 0.954, 1.80  
 1.80, 1.42, 0.98, 1.78, 1.34, 1.80, 1.08, 1.56  
 . . . . . 0.94, 0.90, 0.94, 0.90, 0.90, 1.84  
 1.86, 1.00, 1.00, 1.24, 1.00, 1.00, 1.24, 1.04, 1.00, 1.30, 1.84

The diastolic pause after the first systole of a group is longer than that after the second; this is usually longer than that after the third and subsequent systoles. There is no lessening of the frequency of the ventricular rate towards the end of a group comparable to that recorded by Wenckebach (83). The jugulo-carotid tracing in Fig. 6 demonstrates that during the group-beating of the ventricles the auricles were in constant, rapid, rhythmic flutter at a rate of about 276.9 per minute.

In some respects this case resembles more closely that recorded by Hertz and Goodhart (29) than any other in the literature. In their case of auricular tachycardia with a rate of about 234 per minute the rhythm of the ventricles was 'most frequently bigeminal', and the ventricular rate varied from 44 to 170 per minute, the latter rate being attained after the administration of atropine.

The coupled rhythm and group-beating of complete auriculo-ventricular heart-block is discussed on page 75.

iii. *Coupled rhythm with perpetual arrhythmia (continual irregularity) of the ventricles.* In most cases of perpetual arrhythmia, the ventricular rhythm is wholly disorderly. In some instances, however, the ventricular beats become linked in pairs. While the interval between the first and second beats of each couple is usually constant, that which separates the second beat from the first beat of the next couple remains inconstant, and thus a coupled rhythm is super-added to the perpetual arrhythmia.

Considered from this aspect, cases of perpetual arrhythmia may be divided

into two groups:—(a) that in which the superadded coupled rhythm is seldom if ever met with in series for any length of time, the coupled rhythm being a transient and, apparently, accidental event; and (b) that in which a coupled rhythm of the ventricles is more readily induced and more permanent. Mackenzie (56) has shown that the cases of the second group are old rheumatic cases (not those secondary to cardio-sclerosis associated with arterial degeneration), and that the coupled rhythm may be induced by administration of digitalis.

An example of the first group is shown in Fig. 7 from a man (Case III), aged 40, who had suffered from acute rheumatism at the age of eighteen and from syphilis at the age of twenty. Nine years later, while on active service in South Africa, he began to complain of slight palpitation. Since then, however, he was always able for his work as a dock labourer or coal-miner, until one day, when he was hurrying up a long incline in the pit, he was seized with sudden and severe breathlessness and palpitation. A fortnight later he was admitted to the wards in the Edinburgh Royal Infirmary under the care of Dr. Bruce, who has kindly permitted us to refer to the case. The apex-beat was in the sixth left intercostal space, five and a half inches from the midsternal line, while the right border of the heart lay two inches to the right of the midsternum. A loud mitral systolic, a softer mitral diastolic, and an aortic systolic murmur were audible, while the second sound was accentuated all over the precordia. There was evidence of oedema of the lungs but not of the limbs.

The arterial pulse was continually irregular. A portion of one of the tracings, taken four days after the patient's admission to hospital, and two days after he had begun to take five minims of tincture of digitalis four-hourly, is reproduced in Fig. 7. The intersystolic periods in the cardiogram were 0.40, 0.40, 0.44, 0.62, 0.43, 0.44, 0.96, 0.36, 0.56, 0.64, 0.66, 0.40, 0.64, 0.40, 0.36, 0.50, 0.54, 0.56, 0.68, 0.36, 0.40, 0.36, 0.40 $\frac{3}{4}$ , 0.78, 0.66, 0.42, 0.56, 0.42, 0.60, 0.60, 0.36, 0.50 seconds. These figures show that the intersystolic period before one or more coupled beats is in some instances relatively long (0.96, 0.68, and 0.66). In other tracings from this patient, coupled beats were even less frequently present, and even after the administration of digitalis had been continued for several days the coupled rhythm never became pronounced.

An example of the second group, with a more permanent coupled rhythm superadded to a perpetual arrhythmia, is given in Fig. 8. The patient (Case IV) was a woman, aged 49, under the care of Dr. Byrom Bramwell, to whom we are indebted for the opportunity of recording the case. She had suffered from scarlet-fever at the age of five, but had never suffered from rheumatism or syphilis. Her heart, she stated, had always been 'weak', but especially so since the menopause. For the last five months she had been more breathless, the feet had begun to swell, she had palpitation and precordial pain on exertion and vertigo on rising from the recumbent posture. She was admitted to the Edinburgh Royal Infirmary suffering from marked dyspnoea and general oedema. The right and left borders of the heart were one and a half and five and a half inches respectively from the midsternal line. A rough systolic

murmur of mitral origin was audible, and an aortic systolic murmur of lower pitch was also present. The urine contained albumin.

When the patient was admitted to hospital the pulse was continually irregular, and its rate was 96 per minute; the arteries were thick and tortuous, and the systolic blood-pressure was equal to 140 mm. Hg. She was given ten minims of tincture of strophanthus thrice daily. Eight days later the rate of the cardiac impulse, and of the arterial pulse, was from 64 to 80 per minute. Four days later a coupled rhythm of the ventricles started, and on the following day tracings, a portion of which is reproduced in Fig. 8, were taken. The pulse wave in the radial arteries was of small volume, and the second beat of each couple was so feeble that it almost seemed as if the radial pulse was only half as frequent as the cardiac impulse. When one auscultated the heart, the first systolic murmur after a long diastole was followed by a closed second sound. This was quickly succeeded by another systolic murmur and closed second sound before the long pause recurred. No presystolic or diastolic murmurs were audible over any part of the precordia.

In Fig. 8 the coupled rhythm is best shown in the cardiogram. In the sphygmogram the second beat of each couple is small and coincides with the instant at which the dicrotic wave of the first beat should appear. In the jugulo-carotid tracing there is a ventricular venous pulse with each beat of each couple. The intersystolic periods in the cardiogram of Fig. 8 are 0.41, 0.92, 0.41, 1.28, 0.41, 0.86, 0.41, 1.20, 0.40, 1.24, 0.41, 1.26 seconds. In other tracings obtained on the same day the corresponding figures were 0.42, 1.16, 0.46, 1.06, 1.42, 1.10, 0.42, 0.98, 0.48, 0.42, 0.70, 0.42, 0.42, 1.02, 0.42 seconds; and again 0.44, 1.34, 0.44, 1.30, 0.44, 1.30, 0.44, 1.20, 0.44, 1.32, 0.44, 0.94, 0.40, 1.20 seconds. It is evident, therefore, that whereas in any one record the interval between the first and second beats of each couple is fairly uniform, the diastolic pause after the second beat of each couple is of variable duration, and consequently although there is a coupled rhythm there is also a perpetual arrhythmia of the ventricles.

On the day that the tracings in Fig. 8 were taken, the dose of tincture of strophanthus was reduced to five minims thrice daily. The coupled rhythm persisted until four days later, when it gradually disappeared. Thereafter the pulse was continually irregular, with a rate of about eighty per minute, until the patient, being much relieved, left hospital.

Numerous records of this form of coupled rhythm are given by Mackenzie (49, 56), and cases are recorded by Gerhardt (Figs. 5 a, 5 b, and 10), Hering (26) (Case IV of his series), Hay (23), and Norris. The case of 'hemisystolic bradycardia' recorded by Balfour (2) is probably of the same nature.

The explanation of this form of coupled rhythm will be discussed in a later part of this paper (see page 82).

Fig. 9, or the coupled rhythm may be more persistent, as in the patients from whom the tracings, which are reproduced in Figs. 10, 11, 12, and 13, were obtained.

The tracings in Fig. 9 were obtained from a patient (Case V) under the care of Dr. G. A. Gibson, who has kindly given us permission to refer to the case. The patient, aged 49, had been suffering for some months from dyspnoea, dropsy, cyanosis, insomnia, and other symptoms of cardiac failure. The ventricular rhythm was usually regular, but sometimes there were short series of coupled ventricular beats. In Fig. 9 the intervals between the carotid waves are 0.52, 1.00, 0.56, 1.00 seconds, and again 0.54, 1.04, 0.52, 0.94 seconds. In Fig. 9, after two interauricular periods of 0.75 second, the auricular rhythm remains constant at 0.79 to 0.80 second, being unaffected by the extra-systoles of the ventricles. This fact alone suggests that the extra-systoles are ventricular rather than 'nodal' in origin. Moreover, when an extra-systole occurs, there is a large positive wave in the jugulo-carotid tracing, with a notch on its line of descent to indicate the carotid wave. It is evident, therefore, that the waves *a* and *c* occur almost synchronously. Now we know that whereas the commencement of the *a* wave coincides almost exactly with the commencement of auricular systole, the normal Vs-*c* interval is on an average from 0.05 to 0.07 of a second, and that in the case of an extra-systole it is appreciably longer because of the longer presphygmic period. We must therefore conclude that in the second beat of each couple in Fig. 9, where the *a* and *c* waves are more or less fused in one, the ventricular contraction started before the auricular. The second beat of each couple is therefore an extra-systole of the ventricles which does not disturb the auricular rhythm, and it is therefore a ventricular extra-systole.

A more persistent coupled rhythm, in which the second beat of each couple is a ventricular extra-systole, is represented in Fig. 13. The tracings were obtained from a man (Case VI), aged 33, who had suffered acute rheumatism seventeen years previously, and who, three months before he came under our observation, had been confined to bed for five weeks with an attack of influenza. He presented a soft mitral systolic murmur; the radial arteries were thick; the blood-pressure estimated by Martin's modification of the Riva-Rocci sphygmomanometer varied between 100 mm. and 130 mm. Hg.; and the urine, although free of albumin, contained a few hyaline and granular casts. Throughout the four months during which the patient was under observation he always had the appearance of good health, and he was able to walk several miles daily without being either fatigued or distressed. At no time was he given digitalis.

When the patient first came under observation the rate of the heart was 48.3 per minute; jugulo-carotid tracings presented *a*, *c*, *v*, and *h* waves with each beat; the *a*-*c* interval was 0.2 of a second; and there was slight sinus irregularity. A fortnight later the ventricular rate was 42 to 43.6 per minute. There were many extra-systoles in which the auricle and ventricle were in contraction simultaneously, although the ventricle began to contract before the auricle. In some of the tracings taken on this occasion extra-systoles occurred singly, or in series of twos or threes. In other tracings there was a coupled

rhythm. This is shown in Fig. 13, where the intersystolic periods in the cardiogram are 1.20, 1.60, 1.20, 1.55, 1.25, 1.55, 1.20, 1.60, 1.20, 1.60 seconds. In another tracing taken on the same day the ventricular intersystolic periods were 1.00, 1.62, 1.16, 1.60, 1.18, 1.62, 1.16, 1.64 seconds.

Three days later the ventricular rate was 40.2 per minute, with intersystolic periods of 1.30, 1.66, 1.40, 1.71, 1.45, 1.40, 1.70, 1.42, 1.65, 1.22, 1.65, 1.53, 1.13, 1.80, 1.50 seconds. On this occasion the ventricular arrhythmia was obviously due to partial auriculo-ventricular heart-block; but there was also some sinus irregularity and an occasional ventricular extra-systole.

A week later the ventricular rate was 43.6 per minute; its rhythm was irregular owing to partial auriculo-ventricular heart-block, and to an occasional extra-systole which did not disturb the auricular rhythm.

Eleven days later the auricles were beating 63 times per minute; there was partial auriculo-ventricular heart-block, and the ventricular irregularity was further intensified by the occurrence of many extra-systoles, which, however, did not disturb the rhythm of the auricles.

Fourteen days later the ventricular rate was 48.6 per minute. The intersystolic periods in one tracing were 0.93, 1.55, 1.20, 0.92, 1.50, 1.22, 1.55, 1.20, 0.92, 0.92, 1.50, 1.38 seconds. Two, three, four, or five stimuli in succession reached the ventricles, but the third, fourth, fifth, or sixth stimulus respectively was blocked. Two months later every third stimulus to the ventricles was blocked. The first  $\alpha$ -Vs interval after the block was 0.53 of a second, the second  $\alpha$ -Vs interval was 1.01 of a second, and the ventricles were beating 39.4 times per minute and quite regularly except for an occasional single extra-systole. The patient had no syncopal or epileptiform seizures at any time while he was under observation.

One of the tracings showing the coupled rhythm in this case is reproduced in Fig. 13. With the first beat of each couple the jugulo-carotid tracing presents  $a$ ,  $c$ , and  $v$  waves. The  $\alpha$ -Vs interval is 0.12 of a second; the  $a$ - $c$  interval is 0.20 of a second, and the Vs- $c$  interval is 0.08 of a second. The first beat of each couple is therefore a normal beat of the heart. With the second beat of each couple there are two large waves marked  $a + c$  and  $v$  in the jugulo-carotid tracing. The moment at which the  $v$  wave terminates is synchronous with the lowest point (marked 6 in the tracings) on the cardiogram. The wave in question therefore terminates at the moment of opening of the auriculo-ventricular valves, and is consequently the ventricular wave.

The large, broad-summit wave, marked  $a + c$ , commences about 0.11 of a second after the start of the corresponding ventricular systole as determined on the cardiogram. As the ventricular contraction is premature the Vs- $c$  interval cannot be less than 0.08 of a second—the Vs- $c$  interval of the first beat—and will almost certainly be appreciably longer in virtue of a longer presphygmic period. Consequently the upstroke of the  $a + c$  wave is probably due in part to the carotid wave. But at the moment when the  $a + c$  wave starts, an auricular systole is due, and the wave is therefore also due in part to



auricular systole. The large size of the wave is thus due to two factors, (1) contraction of the right auricle while the ventricle is in systole and the tricuspid valve is closed, and (2) superposition of the *a* and *c* waves.

We therefore conclude that when the tracings in Fig. 13 were taken the auricles were beating almost if not entirely rhythmically, and the coupled rhythm of the ventricles was due to regularly recurring ventricular extra-systoles which did not disturb the auricular rhythm.

Tracings from a third case of coupled rhythm in which a ventricular extra-systole recurs after each physiological beat are reproduced in Figs. 10, 11, and 12. They were obtained from a patient (Case VII) who was suffering from infective endocarditis of the mitral valve. He was a vanman by occupation, aged 24, and had suffered for a fortnight before admission to hospital from indefinite febrile symptoms which ensued immediately after the extraction of a tooth for a 'gumboil'. The patient died from cardiac failure nine days after the occurrence of a cerebral embolus, and four weeks after the onset of his illness.

On the patient's admission to hospital, his pulse was regular and soft, but infrequent. Palpation of the cardiac impulse, which was full and widespread, showed that many of the cardiac contractions were missed at the radial artery; and tracings showed a coupled rhythm (Fig. 10). A mitral systolic murmur was present. The coupled rhythm was recognized on the patient's admission and continued unchanged for nearly twenty-four hours. Thereafter the rhythm was single until the day before death, when it was again coupled for a short time. The transition was not observed, but must have been of short duration. The only irregularity apart from the coupled rhythm occurred about forty-eight hours after admission, when a few couples were noticed. In the tracing taken at that time, the pulse periods in seconds were 0.85, 0.5, 1.20, 0.8, 0.8, 0.55, 1.25, 0.8, 0.8, 0.8, 0.55, 1.20, 0.85, 0.8, 0.5, 1.3, 0.8, 0.8, 0.85, 0.9, 0.9, 0.9, 0.9, 1.0, 0.9. The full periods of the coupled beats were 1.7, 1.8, 1.75, 1.8 seconds. The average period of the single beats was 0.853 of a second, so that the long pause in a couple is fully, or more than fully, compensatory. Jugulo-carotid tracings, unfortunately, were not obtained at that time.

The cardiogram in Fig. 10 shows that the second beat of each couple begins at a constant interval (0.45 of a second) after the commencement of the first beat, and is so premature that its effect upon the radial tracing is hardly appreciable. In the jugulo-carotid tracing (Fig. 11) the first radial beat is synchronous with the wave marked *c*, the upstroke of which commences 0.05 of a second previously. The wave *b* precedes *c* by 0.1 of a second, and *a* precedes *c* by 0.25 of a second. It is probable that *b* does not represent the carotid elevation, for the interval between the wave *b* and the beginning of the radial upstroke being 0.15 of a second it is only slightly less than the Vs-radial interval (0.2 of a second) in Fig. 10. Moreover, the *b*-radial interval (about 0.15 of a second) is considerably longer than the average *c*-brachial interval (0.065 of a second), a period which closely approximates to the actual

time (0.05 of a second) between the wave  $c$  and the onset of the radial beat in Fig. 11. The inference that the wave  $c$  is the carotid elevation is strengthened by the fact that the interval between  $c$  and the notch separating  $v^1$  from  $v^2$  coincides almost exactly with the period between the upstroke of the radial tracing and the second (dicrotic) notch upon its line of descent. The first beat of each couple is thus shown to be normal in all respects except that the  $a$ - $c$  interval is somewhat prolonged.

Following the  $v^2$  wave in Fig. 11 there is a large wave marked  $\frac{a}{c}$  in the jugulo-carotid tracing, and this is sometimes followed by an  $h$  wave. The large  $\frac{a}{c}$  wave is in marked contrast to the minimal corresponding wave (the third wave in the descending line) of the sphygmogram, and is therefore not wholly a carotid wave. A comparison of the apical, jugulo-carotid, and radial tracings indicates that the second beat of each couple occurs synchronously with the wave  $\frac{a}{c}$  of the jugulo-carotid tracing. And further, this tracing demonstrates that the auricles are beating rhythmically. If, as we believe, the  $\frac{a}{c}$  wave is in part an auricular wave, it follows that in the second beat of each couple the auricular contraction is not premature, and the second beat of each couple is a regularly recurring ventricular extra-systole.

Cases of a similar nature have been recorded by Mackenzie (45, 52), Volhard (Case IV of his series), Goteling Vinnis, A. G. Gibson (20), Einthoven, and Strubell.

#### IV. *Coupled Rhythms of Auricles and Ventricles.*

When both the auricles and the ventricles participate in the coupling, the two beats of each couple may be due to stimuli arising in different parts of the heart, or both beats may be due to stimuli from the same part of the heart.

i. *Coupled rhythm in which both auricles and ventricles participate, and in which the two beats are due to stimuli from different parts of the heart.* Case VIII illustrates this form of coupled rhythm, and Case IX is probably of the same nature.

The tracings in Fig. 14 were taken from a man (Case VIII), aged 59, who had been a labourer and coal-carrier, and who had suffered from acute rheumatism twenty-five years previously. His radial arteries were thick; a systolic murmur was audible at the mitral area; and he had some dyspnoea on exertion. The urine did not contain any albumin. When the tracings in Fig. 14 were obtained, the patient was suffering from an attack of bronchitis. In Fig. 14 after five normal, rhythmic beats in which the  $a$ - $c$  interval is 0.2 of a second, there is a premature beat of auricle and of ventricle. The first physiological beat after the long pause is followed by another premature beat which is represented by a large wave  $a+c$  in the jugulo-carotid tracing. After the next physiological beat there is again a premature, and almost synchronous, contraction of auricle and ventricle, after which the heart reverts to a normal rhythm. In Fig. 14 the pulse periods estimated from the brachial tracing are 0.86, 0.86,

0.87, 0.86, 0.53, 1.10, 0.60, 1.02, 0.60, 0.95, 0.80, 0.73, 0.73, 0.73, 0.73, &c., seconds. Thus when the coupled rhythm occurs, the post-extra-systolic pause is not fully compensatory; and the rate of the heart is somewhat accelerated after the coupled rhythm ceases.

Two months later, this patient's heart was beating rhythmically 81.08 times per minute, and the  $\alpha$ -Vs interval was 0.12 of a second.

Another case, probably of the same nature, was a man (Case IX), aged 55, a retired schoolmaster, who was under the care of Dr. Byrom Bramwell, to whom we are indebted for permission to refer to the case. Although the patient, having found his professional work too exacting, had retired therefrom seven years ago, he had been in good health for thirty years and had never suffered from acute rheumatism or any venereal affection. While on the top of a tramway-car, he was suddenly seized with a 'chill' in the epigastrium, accompanied by a sensation of 'stiffness' in the same region. He returned home, breathless, but without any pain or palpitation. A fortnight later, when he was admitted to the Edinburgh Royal Infirmary, the patient was markedly cyanosed and breathless, with some oedema of his back, with a right-sided hydrothorax, and with insomnia. The radial arteries were thick, and the pulse was irregular. The patient was given either  $\frac{1}{100}$  of a grain of digitalin or five minims of tincture of digitalis every four hours, and after he had been in hospital for a week, his general condition was materially improved, and the amount of urine passed in twenty-four hours had risen from sixteen to fifty ounces.

Tracings taken on the seventh day after the patient's admission to hospital showed that the rate of the pulse in the brachial arteries, and of the cardiac impulse, was sometimes 92.3 per minute (see Fig. 15). On these occasions there was one cardiac impulse for each arterial pulsation, and the rhythm was regular. On auscultating the heart, one heard closed first and second sounds without any murmurs.

At other times on the same day the pulse rate was only 58.8 per minute, but there were two cardiac impulses for each arterial pulsation. As is shown in the tracing from the apex-beat (Fig. 16), the first systolic rise in the cardiogram is followed after an interval of 0.4 of a second by a second systolic rise, after which there is a diastolic pause longer than that following the first beat. On auscultating the heart, one now heard three sounds (lub, dup, lub) for each arterial pulse. The first and third sounds coincided with systolic impulses at the apex-beat; the third sound was followed by a long pause. It was evident therefore that the second systolic impulse and the third sound represented a premature ventricular systole, which occurred so early in diastole after the first beat that it failed to open the aortic valves and thus failed to cause a second sound or an arterial pulse wave.

Transitions from the more frequent to the slower rate of the arterial pulse are recorded in Fig. 26. From what has been already said, it is evident that the coupled beats in this figure do not correspond to coupled beats of the

ventricles, but that the longer pause on each occasion is due to a premature beat not being represented by any wave in the sphygmogram.

The exact nature of the coupled rhythm in this case is somewhat uncertain. No satisfactory jugulo-carotid tracings could be obtained. The patient was breathless, and could not lie down in bed, and his sterno-mastoid muscles were contracted. The case does not appear to be one of that group in which a coupled rhythm becomes superadded to a perpetual arrhythmia under the influence of digitalis. It is true that the patient had been taking large doses of digitalis, but he had no valvular lesion, and he had not suffered from rheumatism. Moreover, in cases of perpetual arrhythmia with a superadded coupled rhythm, although the interval between the first and second beats of each couple may be constant, that between the second beat and the first of the succeeding couple is inconstant. The tracings in Fig. 16, however, show that not only is the interval between the first and second beat of each couple constant, but that the interval separating the second beat from the first of the succeeding couple is likewise constant throughout. Further, when the coupled rhythm disappeared, the ventricular action was rhythmic, as is shown in Fig. 15. The day after these tracings were obtained the dose of digitalis was reduced, the coupled rhythm disappeared, and the ventricles became markedly arrhythmic for a few days. Thereafter the rhythm gradually became perfectly regular, and the patient made a good recovery.

We regard this case as probably an instance of that form in which the second beat of each couple is an extra-systole. The ventricular intersystolic periods in Figs. 15, 16, and 26 indicate that the pause after the first beat of each couple is not fully compensatory, and consequently if the premature beats are extra-systoles they are probably of 'nodal' or auricular origin rather than ventricular.

When we speak of 'nodal' extra-systoles as distinguished from auricular extra-systoles, we are following Mackenzie's (50, 51) classification. In an auricular extra-systole, both auricle and ventricle contract prematurely, but the auricular contraction precedes the ventricular, and in consequence of delay in the transmission of the stimulus from auricle to ventricle and the longer presphygmic period  $a$  precedes  $c$  by a longer period than obtains in a physiological beat. In a 'nodal' extra-systole, although both auricle and ventricle contract prematurely, there is only a single large wave in the jugulo-carotid tracing which Mackenzie interprets as evidence of simultaneous contraction of auricle and ventricle, and which he suggests may be due to the stimulus arising at, or in the neighbourhood of, the auriculo-ventricular node. In our opinion, the necessarily long presphygmic period associated with an extra-systole makes it probable that in a 'nodal' extra-systole the ventricle commences to contract *before* the auricle.

In some extra-systoles the  $a$ - $c$  interval is much shorter than normal, though both auricle and ventricle contract prematurely. We suggest that when the  $V_s$ - $A_s$  interval is so short that  $c$  occurs very soon after  $a$  (see Fig. 12), the

stimulus originates at a higher level in the auriculo-ventricular bundle (perhaps in the neighbourhood of the  $a-v$  node) than is the case when the  $a$  and  $c$  waves are fused together.

A tracing (Fig. 12) taken from Case VII seven days after the tracings in Fig. 11 had been obtained, and at a time when the cardiac action was regular and frequent, shows only two waves, and if they represent  $a$  and  $c$ , the  $a-c$  interval is only 0.06 of a second, and  $b$  is no longer present. As will be seen in a paper published by one of us (5) the node of Tawara was found to be involved in an inflammatory lesion, whereas the auriculo-ventricular bundle was intact. While we do not feel justified in defining the exact site of origin of the stimuli with this rhythm, it is evident that, as the  $a-c$  interval is so short and as the presphygmic period must be taken into account, the ventricles presumably must have started to contract together with, or even before, the auricles. We may therefore conclude that the stimuli causing each beat in Fig. 12 arise at some part of the heart whence they can be transmitted rapidly to the musculature both of the auricles and of the ventricles, causing all the chambers of the heart to contract more or less synchronously.

The relation of the  $a$  and  $c$  waves in the jugulo-carotid tracings of extra-systoles is dependent, however, upon other factors than the mere time-relations of Vs and As. As Robinson and Draper point out, a weak cardiac contraction is followed by a prolonged presphygmic interval. Further, the earlier the extra-systole the less active is the conduction and the longer is the presphygmic interval. The time relationship of the extra-systole to the preceding physiological beat is therefore important, and the earlier the extra-systole the later will be the appearance of the  $c$  wave in the jugulo-carotid tracing.

Cases with a regularly recurring 'nodal' extra-systole have been recorded by Mackenzie (53), Laslett, Rautenberg, and Norris (Case IV of his series). Gerhardt's case of 'hemisystole' may probably be included in this group. Case III of Volhard's series is spoken of as a 'Pseudo-alternans bigeminus from auricular extra-systoles' and as 'auricular bigeminy'; but in Fig. 7 of Volhard's paper, although both auricle and ventricle contract prematurely in the second beat of each couple, the  $a-c$  interval is shorter than that of the first beat. We therefore regard the case as a coupled rhythm with a recurring 'nodal' rather than 'auricular' extra-systole. A regularly recurring 'nodal' extra-systole was observed by Cushny (8) in a dog under the influence of aconitine.

We have not observed any instance of a coupled rhythm in which the second beat of each couple was undoubtedly a regularly recurring auricular extra-systole. Five cases are recorded in the literature:—(1) Volhard's case; which we have just discussed. (2) The first case of Hering's (26) series, and (3) Wenckebach's (78) case. In both these cases, as in Case IX of our series, the pause after the second beat of each couple was not fully compensatory, and the extra-systoles were therefore supposed to have arisen in the auricle. But no jugulo-carotid tracings are recorded, and therefore we cannot be certain whether

the second beat of each couple may not have been a 'nodal' rather than an 'auricular' extra-systole. (4) The case recorded by Carrión and Eizaguirre. In Fig. 9 of their paper the  $\alpha$ -c interval of the second beat of each couple is not longer, but on the contrary shorter, than that of the first beat. (5) The transient coupled rhythm in the case of paroxysmal tachycardia recorded by Lewis (40). In Fig. 17 Lewis considers that the bigeminy consisted of 'normal beats and auricular extra-systoles'.

ii. *Coupled rhythm in which both auricle and ventricle participate, and in which both beats of each couple are due to stimuli from the same part of the heart.* This is the condition which Wenckebach (80) designates true bigeminy of the heart. The following case illustrates this form of coupled rhythm.

The patient (Case X), a painter by trade, aged 44, had never suffered from any serious illness until, six months before his admission to hospital, he began to complain of dyspnoea, cough, and dropsy. When admitted to hospital the patient was cyanotic and dropsical, and there was a large pleural effusion on the right side. The heart was considerably enlarged both to the right and to the left. Double murmurs of aortic origin were present, and there was probably mitral reflux as well. The urine contained a considerable amount of albumin. The patient's condition was extremely critical for a few days, and even after improvement did occur compensation was never fully restored, and although he was able to walk about without discomfort during the later part of his residence in hospital, he became breathless on the least exertion and was never able to lie down flat in bed at night.

Notwithstanding the serious degree of cardiac failure, the pulse rate was never rapid, and was usually about eighty per minute. The coupled rhythm was first noticed twelve days after admission, and recurred at longer or shorter intervals throughout his residence in hospital. The incidence and duration of the coupled rhythm was variable. At first it came on frequently and lasted for a considerable time. Later it only occurred at longer intervals, and lasted for shorter periods, sometimes for not more than ten minutes. Change of posture, variations in respiration, muscular effort, &c., were all at this time apparently effective in checking the coupled rhythm, whereas at first they had no such effect. We were never able, however, to induce a coupled rhythm when the heart was beating regularly. Digitalis was administered to this patient only for a few hours after his admission to hospital, and had not been given for more than ten days before the coupled rhythm was first noticed.

Tracings showing the commencement and termination of the coupled rhythm were obtained on several occasions. The change in every instance was abrupt. In Fig. 21 the radial pulse periods are at first 0.95, 0.95, 0.90, 0.90, 0.90, 0.90 seconds, and this is suddenly succeeded by periods of unequal length, namely, 0.65, 1.15, 0.55, . . . . . 1.25, 0.6, 1.25, 0.55, 1.25, 0.55, 1.20 seconds. In another tracing periods of 0.75, 0.75, 0.75, 0.7, 0.7, 0.75, 0.75, 0.8 were followed by 0.55, 1.00, 0.5, 1.00, 0.5, 1.00 seconds. In yet another tracing the periods were 0.85, 0.85, 0.80, 0.85, 0.90, 0.80, 0.7, 1.05, 0.5, 1.15, 0.5, 1.2, 0.55, 1.1,

0.5, 1.15 seconds. Fig. 19 shows the termination of the coupled rhythm which suddenly changes from periods of 0.6, 1.0, 0.6, 1.0, 0.6, 1.0, into 0.8, . . . 0.8, 0.8.

The variations in the pulse periods during the normal rhythm in Fig. 20 make it difficult to say whether the pause after the second beat of a couple is fully compensatory; but in Fig. 21 the pause is fully compensatory. On one occasion a tracing was obtained showing two groups each of three beats amongst the coupled beats. This is shown in Fig. 18. The average duration of the couples is here 1.47 seconds, and that of the group of three beats is 2.25 seconds, which is slightly longer than three times the theoretical normal period, 0.735 of a second.

As the pause after the second beat of the couples in Fig. 21 is fully compensatory it would appear as if the second beat were a ventricular extra-systole. The jugulo-carotid tracings, however, indicate that this is not the case, but that both beats own the same origin. In Figs. 18, 19, 21, and 22, the waves marked *c* occur 0.05 of a second before the radial, and thus record the carotid beats. The waves marked *a* are auricular waves which occur 0.1 of a second before the carotid waves. In Fig. 18 the short *a-c* interval is also apparent with the third beat of the group of three, and it also obtains when the rhythm was regular as in Fig. 20.

The *a-c* interval, therefore, is short (0.1 of a second) in all the tracings. Although such a short *a-c* interval is not uncommon in sinus rhythms with a frequent rate of the heart, it is unknown with a pulse rate of 66. And when the presphygmie period is taken into account, the As-Vs interval is probably too short for the normal sinus, auricle, ventricle sequence. We therefore suggest that the stimuli in this case originate at a lower level than the sinus, and yet above the level at which ordinary ventricular extra-systoles arise (compare p. 69).

#### V. *Chief Clinical Features of the Cases Recorded.*

In all the cases of our series presenting a coupled rhythm there have been signs of mitral regurgitation or evidence of cardiac failure. We have never observed a coupled rhythm in an individual who did not manifest some evidence of cardiac weakness. The cases in which the coupled rhythm was long maintained were cases of pronounced heart failure; but in others, for example Case V, presenting a coupled rhythm for shorter periods, the degree of heart failure was almost as severe. With the exception of Case IX, in which the ventricular rate was 92.3 per minute, and the cases of auriculo-ventricular heart-block, the ventricular rate was of moderate frequency. Some of our cases were taking digitalis, others were not.

#### VI. *Explanation of Coupled Rhythms.*

We have already discussed the causation of coupled rhythm of the ventricles in partial auriculo-ventricular heart-block. The remaining forms of coupled rhythm still require consideration.

Several theories have already been brought forward as an explanation

of coupled rhythms, but none of them are wholly satisfactory, for, as we have shown, coupled rhythms are of various kinds.

The association of a coupled rhythm with digitalis has been discussed by many writers, amongst whom mention may be made of Lorain, Huchard, Fauconnet, Henschen, and Merklen. A coupled rhythm, it is generally agreed, is most commonly met with in cases of mitral disease with an enfeebled heart and a pulse rate which is infrequent from full doses of digitalis. Henschen has suggested that in these cases, on account of the prolongation of diastole produced by the drug, the auricles are incompletely emptied at their regular systole. With the succeeding ventricular systole the reflux from the ventricle still further distends the left auricle, and the excessive pressure which results incites the auricles to contract prematurely. But as their contraction occurs before the ventricles are properly distended the contraction of the latter produces only a feeble wave in the aorta. Following the extra-systole, the auricular excitability is so far reduced that a complete distension of their cavities is required to evoke a new contraction, and the succeeding diastole is in consequence prolonged and more or less compensatory. Henschen's theory is plausible, and with some modification would be applicable to cases of coupled rhythm in which the second beat of each couple was a regularly recurring auricular extra-systole. But if a regularly recurring auricular extra-systole does occur, it is evidently a rare phenomenon, and we know that the second beat of each couple is most frequently a ventricular extra-systole.

Wenckebach (80, 82) considers that the term 'true bigeminy of the heart' should be confined to cases of coupled rhythm in which both auricles and ventricles participate in the coupling, and in which both beats are due to stimuli arising from the same part of the heart. One explanation of 'true bigeminy', he says, would be an undue prolongation of the stimulus which lasted so long that it outlived the initial contraction and refractory period, and so produced the second beat. But as all the available evidence indicates that the stimulus material is completely destroyed by each successive contraction, this theory cannot be accepted. Wenckebach's second and more tenable explanation is that, from defective excitability, some of the muscle fibres in the immediate vicinity of the venous ostia fail to react to the primitive stimulus; but with the steady increase of excitability during their prolonged diastole these fibres eventually respond and so initiate the second beat. Wenckebach also suggests that a similar result might ensue from a local and partial failure of conductivity at the basal part of the heart, leading to dissociation of muscle fibres in this region. We must admit that such dissociation may occur as the result of myocarditis or of functional disturbance from vagal stimulation. A latent dissociation in the sino-auricular region may perhaps be revealed or intensified by the administration of digitalis. If we grant that dissociation of muscle fibres in the basal portion of the heart be possible, it seems reasonable to conclude that some of the fibres in that region may not contract until a later period than other fibres, that both of these



basal contractions may be followed by contraction of auricle and of ventricle, and that a coupled rhythm of the whole heart may thus ensue. Wenckebach's explanation of 'true bigeminy' may be correct, but it is applicable only to one form of coupled rhythm, not to all. We agree with Hering (27), who states that there is no essential difference between a 'sporadic bigeminus' and 'continual bigeminy', for both depend on extra-systoles.

We are inclined to believe that all coupled rhythms, whatever their nature (except some of those in auriculo-ventricular heart-block), may be produced by a similar mechanism, and we will state our theory in general terms:—*Whenever an enfeebled heart is unduly irritable in an abnormal site, any excessive rise of intracardiac pressure may produce a regularly recurring premature systole which originates in the irritable area.*

At the present time it is generally believed that every part of the cardiac musculature possesses the inherent property of initiating rhythmic contractions which may spread from the site of origin over the whole of the heart. In normal individuals the contraction originates near the great veins, and the usual sequence of events, contraction of sinus, auricle, and ventricle, is supposed to be due to the rate of stimulus-production being more frequent in the sinus than elsewhere, the auricular and ventricular rhythms of slower rate never having the chance of obtruding *their* rhythm on the heart.

We know that the rate of stimulus-production in the sinus may vary greatly from causes of a general kind (emotion, exercise, debility, fever, &c.), and that the response of the heart to rhythmic sinus stimulation may be interrupted by contractions arising in the auricle or in the ventricle (extra-systoles). We have little knowledge of the causes of extra-systoles. In some cases they recur frequently; in others they are rare events: in some cases they are observed week after week; in others only for a few days. It is evident, however, that there must be some local cause for their occurrence, some abnormal condition of the tissues where the contraction starts.

Local lesions in the cardiac muscle are extremely common, and originate in several ways: as the result of lesions in the coronary vessels and of inflammation of the endocardium or pericardium, and in the general infections apart from special arterial or inflammatory affections. It is generally agreed that while destruction of tissue involves loss of function, irritation of tissue produces an irritability of function. In meningitis, for example, the early symptoms are those of increased cerebral irritability; those of cerebral depression occur later.

We do not suggest that every extra-systole is due to a local lesion in the musculature of the heart, for the hyperexcitability may be due to functional disturbance in the nutrition of the part involved. But it is suggestive that the cases which notoriously are associated most frequently with arrhythmia are cases of mitral disease and of cardio-sclerosis, precisely the types of case in which the cardiac musculature is most frequently seriously damaged. Microscopic examination of the cardiac muscle is but rarely made from this point of view, yet a number of cases have been recorded where the regions of the sino-

auricular and auriculo-ventricular nodes and of the auriculo-ventricular bundle have been found to be damaged when the intrinsic cardiac rhythm was more or less seriously disturbed.

The experimental researches of Knoll and Hering (25) have demonstrated that extra-systoles may be induced by constriction of the aorta or of the pulmonary artery, or by reflex stimulation of the vaso-motor system. Hering also mentions that he has seen in an isolated and somewhat distended rabbit's heart, which was slightly poisoned by magnesium sulphate, the contraction wave passing alternately from base to apex and from apex to base. The latter wave was shown in the graphic record as the smaller second beat of the couple.

In Pletnew's experiments, cardiac arrhythmia was induced by electrical stimulation of the vaso-motor centre. This raised the arterial blood-pressure, and coincident with this the heart's rate was lessened. In twelve out of fifteen cases there was arrhythmia, consisting of extra-systoles, singly, in groups, or persisting for longer periods (continual bigeminy). In all the experiments the extra-systoles were ventricular. In the two instances of continual bigeminy the rise of arterial blood-pressure was sudden. In one case of continual bigeminy the arrhythmia persisted for at least a minute after stimulation was stopped and the blood-pressure had fallen. Pletnew also records the effects of constriction of the aorta. This is followed by slowing of the heart, which beats more forcibly, and soon thereafter extra-systoles occur, followed in turn by longer periods of continual extra-systole—polygeminy—which lasts as long as the aorta is clamped. The heart's rate is meanwhile accelerated.

From a study of electro-cardiograms, Rothberger and Winterberg conclude that extra-systoles may originate in either the right or the left heart according as the pulmonary artery or the aorta be narrowed. These observations, in conjunction with those of Knoll, Hering, and Pletnew, lead to the supposition that extra-systoles may be induced whenever the heart's capacity for work is inadequate to meet the strain thrown upon it. Excessive intracardiac pressure may doubtless be produced in a variety of ways, but it will certainly accompany any undue prolongation of diastole (von Frey), or the synchronous contraction of auricle and ventricle. In the following pages we shall demonstrate that both synchronous contraction of auricle and ventricle and prolongation of diastole may be followed either by a single extra-systole or by a coupled rhythm.

*Synchronous contractions of auricle and ventricle followed by a ventricular extra-systole. Coupled rhythm of the ventricles in complete auriculo-ventricular heart-block.* In many cases of complete auriculo-ventricular heart-block the auricular and ventricular systoles may every now and again occur synchronously without the (dissociated) rhythm either of auricles or of ventricles being disturbed. In some cases, however, whenever auricular systole coincides with that of the ventricles the latter is followed after a short diastole by a second beat. This sequence of events is recorded in Fig. 17. The patient from whom the tracings were obtained was a cabman, aged 66, suffering from arterio-sclerosis, mitral disease, and auriculo-ventricular heart-block. The

case has been recorded elsewhere (21), and it was there shown that the block was sometimes partial, and at others complete, and that it disappeared entirely while the heart was under the influence of atropin. Tracings taken in 1906 (Fig. 17), and electro-cardiograms taken in 1909 by Dr. Jolly, demonstrate that when auricular systole happens to coincide with the beginning of ventricular systole, a ventricular extra-systole follows. In Fig. 17, and in the upper diagram of Fig. 29, which is constructed from an electro-cardiogram, the diastolic pause after the extra-systole is approximately of the same duration as that after the antecedent rhythmic ventricular beats. In the lower diagram of Fig. 30 the first extra-systole is an interpolated one.

In this case, then, of mitral disease and heart-block, when auricular systole happens to coincide with the commencement—but not with the end—of ventricular systole, the usual mitral reflux from ventricle to auricle is lessened in amount, while the auricle is unable to empty its contents into the ventricle. At the termination of ventricular systole, the residual blood in the left ventricle is therefore excessive in amount, and the diastolic influx from the over-full auricle quickly raises the intraventricular pressure to such a height that a ventricular extra-systole ensues.

As a single extra-systole of the ventricles may be induced by synchronous contraction of auricle and ventricle in auriculo-ventricular heart-block, it might be supposed that some instances of continued coupled rhythm of the ventricles recorded in complete auriculo-ventricular heart-block might possibly be due to an auricular systole invariably coinciding with the first ventricular beat of each couple. Unfortunately the jugulo-carotid or apical tracings that have been published do not always afford conclusive evidence either to prove or disprove this hypothesis. The explanation, however, seems to be applicable to the continual coupled rhythm of the ventricles in the case of auriculo-ventricular heart-block recorded by Vinnis. In Fig. 32 of his paper the auricular rhythm suggests that the auricles were in contraction during the first ventricular beat of each couple. In Figs. 27, 28, 29, and 30, there is no coupled rhythm, and auricular systole seldom occurs during a period of ventricular systole.

In Wenckebach's (82) tracings of coupled rhythm in complete auriculo-ventricular heart-block, the coupled rhythm is evidently not due to synchronous contraction of auricles and ventricles. Wenckebach (82) suggests that to a single stimulus the ventricles respond by two contractions. Lewis and Mack (42) show that in heart-block the electro-cardiogram of the second beat of a couple may be of the same form as that yielded by the first beat. Nicolai and Plesch, however, demonstrate that the second ventricular beat of each couple may yield an atypical electro-cardiogram, and Lewis (38) states that the electro-cardiogram of the second beat may be comparable to that of a ventricular contraction starting in 'an area of ventricular musculature lying to the left and in the neighbourhood of the heart's apex'.

Electro-cardiograms taken by Dr. Jolly from Case II of our series demonstrated that, with the exception of one or two beats in a series of records, the

second ventricular beat of a couple gave the same form of curve as the first beat. Moreover, the beats of the groups were not atypical. The question therefore arises whether the coupled beats, and the group-beating, of the ventricles in Case II may be the expression of an incomplete auriculo-ventricular heart-block. The rate of ventricular contraction (51 to 63 per minute) is suggestive of an incomplete block, and the figures recorded on p. 61, indicating the duration of the intersystolic periods in the groups, are somewhat analogous to those recorded by Wenckebach (79) from cases of partial auriculo-ventricular heart-block. Further evidence in favour of a partial block at the time when the ventricles were in group-beating was afforded by the acceleration of the ventricular rate from 41.02 to 48.2 beats per minute, twenty-one minutes after  $\frac{1}{50}$  of a grain of atropine sulphate had been administered subcutaneously. Four years previously a similar dose of atropine had only increased the frequency of the ventricular rate from 34.88 to 36.58 per minute.

In support of the supposition that the block was still complete during the period of three months while the coupled beats and grouped beats of the ventricles were noticed, we have the evidence of the pre-existing block, persisting for five years and apparently always complete, and that during the nine months that have elapsed since the group-beating was last noticed the ventricular rate has been again fairly constant at about 31 to 36 per minute. If the block were complete, the group-beating of the ventricles may be regarded as analogous to the series of rapid rhythmic ventricular contractions described by Gaskell (17) as following the application of a single stimulus to the auriculo-ventricular ring of muscle, and likewise as analogous to the group-beating of the ventricles after the production of experimental heart-block in dogs 8, 11, and 12 of the series recorded by Erlanger and Blackman.

*Synchronous contraction of auricle and ventricle followed by an auricular extra-systole.* The tracings in Fig. 24 were obtained from a woman, aged 22, suffering from gastric ulcer. She was under the care of Dr. G. A. Gibson in the Edinburgh Royal Infirmary, to whom we are indebted for the opportunity of recording the case. The patient was not taking any digitalis or strophanthus. In Fig. 24 the auricles are seen to be beating rhythmically except that beats V, VIII, and XII are premature. Each of these premature beats follows a synchronous contraction of auricle and ventricle (beats IV, VII, and XI), the coincidence of auricular and ventricular contraction being due to the occurrence of a ventricular extra-systole (V. Ex.). In Fig. 24 the first three beats are rhythmic and the auricular contraction precedes that of the ventricles. The next beat is a ventricular extra-systole occurring at the same time as a rhythmic systole of the auricles. The auricle, contracting while the ventricle is in systole, cannot empty its contents into the ventricle. The succeeding auricular systole is premature and is associated with a premature ventricular beat. A ventricular extra-systole is therefore followed by an auricular extra-systole. The same sequence of events is recorded on two other occasions in Fig. 24, namely beats VII, VIII, and XI, XII.

Another example is recorded in Fig. 23. The tracing was obtained from a woman, aged 36, suffering from acute rheumatism. A partial heart-block of transient character was present. A regular rhythm of 96 beats per minute alternated at times with a much less frequent and irregular pulse, long pauses occurring after one, two, three, or more beats. During the frequent rate the first sound at the apex of the heart was followed by a short, soft, whiff; with the infrequent beats the murmur was longer and louder, replaced a considerable portion of the first sound, and ran for some distance into the short pause. As the tracing shows, during the frequent ventricular rate, the delay in the conduction of the stimulus to the ventricle was so great that ventricular contraction occurred immediately before the succeeding auricular contraction, and at a time when the auricle was already so full that regurgitation from ventricle to auricle could only be minimal, however great the mitral incompetence. With infrequent ventricular beats the prolonged rest restored conductivity to such a degree that ventricular contraction occurred relatively early in relation to the succeeding auricular systole, and at a time when, the auricle being not yet nearly full, a maximal regurgitation was possible and a longer murmur was in consequence audible.

The cause of the irregularity in Fig. 23 is complex. The case is recorded in detail elsewhere (6). A reference to the diagram of Fig. 23 shows that the auricular rhythm is irregular, the As-As periods varying from 0.5 to 0.7 of a second. Conductivity is defective, and the *a-c* intervals vary between 0.3 and 0.5 of a second, and a ventricular contraction frequently drops out. The sphygmie period is plotted out in the diagram, and it is evident that the shorter As-As periods succeed synchronous contractions of auricle and ventricle, the periods being shorter the more nearly do the *commencements* of auricular and ventricular contraction coincide. To As 4, occurring immediately after a ventricular contraction, succeeds an As-As period of 0.7 second; while to As 5, which occurs in the middle of ventricular contraction, succeeds a period of 0.55 second. As 6 occurs apart from ventricular systole, and the succeeding period measures 0.7 second.

An auricular extra-systole following a ventricular extra-systole is recorded by Mackenzie (47).

*Synchronous contraction of auricle and ventricle associated with a coupled rhythm.* From our previous argument, it is apparent that the auricular and ventricular contractions in Case X (Figs. 18, 19, 20, 21, and 22) occur synchronously, the whole heart beating in response to stimuli which arise at a lower level than the sinus and most probably in the auricular musculature. In this case of mitral incompetence, the coincidence of auricular and ventricular contraction entails with each successive systole an incomplete emptying of auricle and ventricle, and consequently, even at the beginning of diastole, an undue distension of auricle and ventricle. If but once, from some change in the respiratory phases, or from some rise of aortic pressure, the requisite degree of auricular distension be too early obtained, a premature contraction will ensue.

This early emptying of the auricle occurs at a time when the venous channels are relatively empty, and a longer pause than before must ensue before the requisite degree of intra-auricular pressure to produce a new contraction is again attained. After the longer interval the venous channels are relatively overfilled, and with auricular diastole the auricle becomes rapidly distended, and an early contraction in consequence succeeds. The coupled rhythm may thus continue indefinitely until from extrinsic causes the flow of blood into the auricle is lessened, and the cardiac contraction occurs with an amount of blood in the various cavities which they are able to expel without distress.

*The relation between coupled rhythms and respiration.* The influence of the respiratory movements upon blood pressure has been recognized for a long time, and many observers have, in consequence, sought to demonstrate a parallel between the respiratory and cardiac rhythms on the assumption that variations in the amount of blood supplied to the auricles might induce variations in the pulse rate. The whole question is discussed fully by von Frey (16), who points out that the respiratory movements have also an *indirect* effect on the blood pressure, for every congestion of blood in the medulla oblongata raises the tone of the vagus centre, and thus accelerates the rate of the heart's contractions. Moreover, moderate distension of the lungs causes reflexly an increased frequency of the pulse. Thus each inspiration is accompanied by an increased frequency of the pulse, and each expiration by a diminished frequency of the pulse. It has been demonstrated repeatedly, however, that the pulse rate in healthy adults is but little altered either with forced or frequent breathing or in full apnoea. In disease, too, the same often holds good. In Cheyne-Stokes respiration, for example, the pulse rate not infrequently varies with the respiratory phases, but although the cardiac periodicity may be as well marked as the respiratory, there is no constant relation between the two. The pulse rate may be increased, slowed, or unaltered during apnoea in different cases, though the variation remains more or less constant in the same individual.

In some cases, however, and especially in childhood and adolescence, an apparently exact relation may be observed. Fig. 27 shows a tracing obtained from a lad, aged 18, who was suffering from acute rheumatism but who presented no evidence of cardiac disease. His pulse was notably irregular, yet the jugulo-carotid tracings presented an auricular venous pulse. In Fig. 27, respiration was performed to order. During the early part of the tracing, the breathing was infrequent and the pulse-beats occur in twos and threes, the pauses between the beats coinciding with those between expiration and inspiration. When the patient held his breath, the pauses became more frequent and separated even individual beats. With more frequent breathing the pulse became accelerated, and rapid, panting breathing almost abolished the irregularity. A single coupled beat is shown in the tracing of Fig. 27, and it suggests that a regular coupled rhythm might have been obtained by careful regulation of the respiratory cycles, but, as this point was not at the time under observation, no actual experiment was made.

Respiratory curves were taken in Cases II, VIII, IX, and X of our series. In Case VIII (Fig. 14) there does not appear to be any definite co-relation between the onset of the transient coupled rhythm and respiration, and the cessation of coupled rhythm during a long expiratory phase may be accidental. In Case IX (Figs. 15 and 16) the onset, duration, and cessation of the coupling were uninfluenced by respiration. In Case X full voluntary respiration occasionally induced a sudden cessation of the coupled rhythm. In this case, however, the rhythm for a considerable time was unstable, and disappeared on change of posture, excitement, &c. We were never successful in our attempts to induce a coupled rhythm when the cardiac action was regular. In Case II the group-beating of the ventricles bore no relation to the respiratory movements.

We have made many observations on the influence of respiration in cases of perpetual arrhythmia. While the pulse rate does appear to be definitely influenced by the respiratory movements, the relation is indefinite and erratic. In a general way, frequent breathing increases both the regularity and the rate of the cardiac action, which during apnoea becomes less frequent and more irregular. In perpetual arrhythmia, coupled beats may occur with any phase of respiration.

*Undue prolongation of diastole causing a single extra-systole.* The first beat after an unduly long diastole is sometimes followed by an extra-systole. This event is shown in Fig. 28, which was taken from a goods porter, aged 47, who was suffering from seborrhoea. His heart was of normal size, the radial arteries were apparently normal, and the cardiac impulse was not unduly forcible. Yet his blood pressure was high (Martin's modification of the Riva-Rocci sphygmomanometer giving a systolic pressure of 180 mm. Hg.), and the second sound at the aortic area was loud and ringing. The pulse was usually rhythmic, its rate being 63 per minute, and the *a-c* interval in the jugulo-carotid tracing was 0.20 of a second. Two extra-systoles are recorded in Fig. 28. After four pulse periods of 1.06, 1.05, 1.05, 1.00 seconds respectively, there comes a longer period of 1.10 seconds, and 0.6 second after the commencement of the succeeding pulse wave there occurs an extra-systole. After the ordinate, the first pulse period measures 1.22 seconds; the beat succeeding the long diastole on this occasion is followed after an interval of 0.53 second by an extra-systole with a post-extra-systolic pause which is not fully compensatory. None of the subsequent pulse periods exceed 1.15 seconds, and there are no more extra-systoles. The condition is analogous to a coupled beat produced experimentally, for the intracardiac pressure must have become unduly high during the long diastole. In the absence of venous and apical tracings we cannot be certain that the extra-systoles were of auricular origin, but as the post-extra-systolic pause after one of them was not fully compensatory, it is probable that both were auricular extra-systoles.

A similar series of events is recorded in Fig. 4, from a patient, aged 48, affected with mitral stenosis and perpetual arrhythmia. The first beat after

a long pause is followed by a premature beat. In tracings recorded by Wenckebach (81) a similar sequence of events is depicted.

*Undue prolongation of diastole producing a regularly recurring extra-systole.* (a) *Of auricular origin*:—Henschen's theory has already been stated (see p. 73). With slight modification it seems to afford a feasible explanation of a coupled rhythm in which the second beat is a recurring auricular extra-systole. In this form of coupled rhythm the auricle is assumed to be unduly irritable and weak, and mitral insufficiency to coexist. In such a case, if diastole be prolonged on but one occasion, the auricles will become over-distended and therefore unable to empty themselves completely with their systole. With ventricular systole and the reflux of blood from left ventricle to left auricle, the latter will be rapidly over-distended, and the excessive intra-auricular pressure will excite a premature contraction of the auricles, followed in due course by a premature ventricular contraction, as is represented in the diagram of Fig. 30. At the time when the ventricular contraction starts, the ventricle is as yet incompletely filled, and the regurgitant blood is this time insufficient to distend the auricle to such a degree as to excite a new contraction, which will only obtain when the next sinus stimulus reaches it. The long diastole which consequently ensues again entails auricular over-distension, and the coupled rhythm will continue indefinitely until from some external influence the flow of blood into the auricle is lessened, and with an auricular contraction of sinus origin no over-distension of its cavity coincides.

(b) *Of ventricular origin*:—In this form of coupled rhythm the ventricle is assumed to be unduly irritable and enfeebled, and mitral insufficiency to coexist. If on any one occasion the diastole of the heart be prolonged (see Fig. 31), the ventricle at the conclusion of auricular systole will be over-distended, and even although the contractility of its musculature has improved during the longer period of rest the ventricle may be unable fully to expel its contents. This failure on the part of the ventricle will be intensified if auricular weakness coexists, and the auricle having been incompletely emptied by its systole the usual mitral reflux had been lessened in amount. At the end of its systole, the ventricle is consequently incompletely emptied, and the diastolic influx from the over-full auricle will rapidly produce so great a degree of distension that the irritable area in the ventricular wall initiates a premature contraction. The prematurity of the systole ensures a complete emptying of the ventricle, for the auricle is still relatively empty, and thus no over-distension of the ventricle will occur before the second sinus stimulus reaches it in the usual manner. But with the lengthened diastole, the ventricle is again over-distended, and the coupled rhythm will continue. An example of a coupled rhythm following a long diastole is recorded by Mackenzie (45).

The essential difference between regularly recurring auricular and ventricular extra-systoles is merely a difference in site of the irritable area, which in one case initiates a premature contraction in the auricle, and in the other in the ventricle.



Cardiac weakness, mitral reflux, and an infrequent pulse from full doses of digitalis are of frequent occurrence. For the production of a coupled rhythm in which the second beat is a regularly recurring extra-systole, a further factor, namely an undue irritability of auricle or of ventricle, is required.

*Coupled rhythm in perpetual arrhythmia.* No satisfactory explanation of a coupled rhythm in perpetual arrhythmia that is applicable to all cases has yet been given.

We know that when the auricles under faradization are in fibrillation, the ventricular rhythm is wholly disorderly. The experimental researches of Fredericq (14) showed that the stimuli exciting the ventricles to disorderly contraction are conducted to them by means of the auriculo-ventricular bundle. The observations of Cushny and Edmunds (9), Mackenzie (50), Hirschfelder (31), and Rothberger and Winterberg, suggested the possibility of perpetual arrhythmia of the human ventricles being associated with auricular fibrillation, and the researches of Lewis (41) have confirmed the accuracy of this hypothesis. The investigations carried out by one of us in conjunction with Dr. Jolly (34) have convinced us that in perpetual arrhythmia the auricles are in the condition known as 'fibrillation'. Whether the musculature of the sinus is fluttering at the same rate as that of the auricles we do not know, but there is no direct evidence of a slower sinus rhythm in electro-cardiograms from cases of perpetual arrhythmia.

In cases of perpetual arrhythmia, the manner in which vagus stimulation, digitalis, atropine, and psychical impressions influence the rate of ventricular contraction indicate that the ventricles are not beating with a ventricular rhythm comparable to that in complete auriculo-ventricular heart-block. This is also indicated by the frequency of the ventricular rate in all the cases except those termed 'nodal bradycardia' by Mackenzie (54). The investigations of Mönckeberg and of Walter Koch have demonstrated that in perpetual arrhythmia the node of Tawara and the auriculo-ventricular bundle may present no signs of disease. Further, electro-cardiograms prove that in perpetual arrhythmia the wave of contraction usually passes over the different parts of the ventricular musculature in normal sequence, for the records seldom present any beats which, according to Einthoven's nomenclature, are 'atypical'. We may therefore conclude that in perpetual arrhythmia, the stimuli for ventricular contraction usually pass to the ventricles by way of the auriculo-ventricular bundle, just as they do when the auricles, under faradization, are in fibrillation.

The distinctive character of the ventricular beats in perpetual arrhythmia with a superadded coupled rhythm can only be elicited by electro-cardiograms, and the records are still too few in number for any general conclusion to be drawn. Lewis (39) states that in two cases of perpetual arrhythmia with a coupled rhythm under the influence of digitalis, the second beat of each couple proved to be of intrinsic ventricular origin. There may perhaps be no essential difference between the coupled rhythm of perpetual arrhythmia and that occurring in hearts in which the auricles are beating in a co-ordinate fashion. All cases of perpetual arrhythmia do not develop a coupled rhythm when substances of the

digitalis group are administered. The well-known effect of these drugs in depressing the conductivity of the auriculo-ventricular bundle suggests that the coupled rhythm following their administration may be a manifestation of an antecedent defect of conductivity which is revealed or intensified by the action of the drug. But it is doubtful whether the coupled rhythm of perpetual arrhythmia can be regarded wholly as the expression of a partial heart-block induced by digitalis or strophanthus. The shortness and the relative constancy of the diastole which separates the first from the second beat of each couple seems almost to preclude the conception of this form of coupled rhythm as a partial heart-block.

It appears more probable that the second beat of each couple arises at a lower level in the heart than that of the first beat. Digitalis in large doses increases the excitability of the heart, and will therefore favour the occurrence of extra-systoles. Moreover, the drug lessens the frequency of the ventricular beats. This effect is probably in part due to vagus stimulation leading to depression of conductivity in a damaged auriculo-ventricular bundle, and perhaps may be due in part to a rise of the arterial blood pressure under the influence of digitalis. But the lessened frequency of the ventricular rate, however it be produced, entails prolongation of ventricular diastole, and consequently increased intraventricular pressure. In an earlier part of this paper we have demonstrated that when the auricles are contracting in a co-ordinate manner the first ventricular beat after a prolonged diastole may be followed by a single extra-systole, or that the prolonged diastole may be followed by a coupled rhythm in which both auricle and ventricle participate.

We suggest that in the coupled rhythm of perpetual arrhythmia the second beat of each couple may likewise originate in the ventricles, and that the second beat will usually yield an 'atypical' electro-cardiogram. Further information on this point is still required. We do know that the coupled rhythm of perpetual arrhythmia is observed in cases of mitral disease with an enfeebled heart and a relatively infrequent ventricular rate owing to digitalis or strophanthus. We know that these are important factors in determining the onset of a coupled rhythm in a heart with the auricles beating in response to a fundamental and dominant sinus rhythm, and it is probable that the coupled rhythm of the ventricles in perpetual arrhythmia differs therefrom only in so far as the auricles are in the one case in fibrillation, and in the other are contracting in a co-ordinate manner.

We have much pleasure in acknowledging the assistance given to us by numerous Residents in the Royal Infirmarys of Edinburgh and Glasgow, and thank particularly Drs. L. Storey, R. J. Binning, J. W. MacLeod, A. R. Paterson, E. G. Glover, J. L. Cochrane, H. F. Smith, Maxwell Ross, and W. F. Buist.

In conclusion we desire to avail ourselves of this opportunity of recording our grateful indebtedness to Dr. James Mackenzie for much personal help and encouragement in our study of diseases of the heart.

## SUMMARY.

Coupled rhythms of the heart may occur from various causes. They are often due to a regularly recurring extra-systole, which is most frequently of 'ventricular' origin.

Synchronous contraction of auricle and ventricle, and an undue prolongation of diastole, necessarily produce an increase of the intracardiac pressures, and are often followed by a premature systole.

It is suggested that, whenever an enfeebled heart is unduly irritable in an abnormal site, any excessive rise of intracardiac pressure may induce a regularly recurring premature systole which originates in the irritable area.

The coupled rhythm so often noticed in cases of 'perpetual arrhythmia' under the influence of substances of the digitalis series, is probably produced by a mechanism similar to that of the coupled rhythms in which an extra-systole recurs after each physiological beat.

## REFERENCES.

1. Bachmann, *Amer. Journ. Med. Sci.*, 1908, cxxxvi. 674.
2. Balfour, *Clinical Lectures on Diseases of the Heart and Aorta*, Third Edit., Lond., 1898, 275, 277.
3. Bard, *Journ. de physiol. et de path. gén.*, Paris, 1906, viii. 466; *Sem. méd.*, Paris, 1908 xxviii. 265.
4. Carrión and Eizaguirre, *Rev. clín. de Madrid*, 1909, ii. 361.
5. Cowan, Kennedy, Paterson, and Teacher, *Quart. Journ. Med.*, Oxford, 1910-11, iv. 35.
6. Cowan, *Proc. Royal Soc. Med.*, Lond., 1910, iii. Therap. and Pharmac. Sect., 101.
7. Cowan, McLeod, and Paterson, *Quart. Journ. Med.*, Oxford, 1909-10, iii. 115.
8. Cushny, *Heart*, Lond., 1909, i. 1.
9. Cushny and Edmunds, *Studies in Pathology*, Aberdeen, 1906; *Amer. Journ. Med. Sci.*, 1907, cxxxiii. 66.
10. Einthoven, *Arch. internat. de physiol.*, 1906-7, iv. 132, Fig. 30; *Arch. f. d. ges. Physiol.*, 1908, cxxii. 517, Fig. 40.
11. Erlanger and Blackman, *Heart*, Lond., 1910, i. 177.
12. Fauconnet, *Münch. med. Woch.*, 1904, li. 2277.
13. Finkelnburg, *Deutsch. Arch. f. klin. Med.*, 1905, lxxxii. 586.
14. Fredericq, *Arch. internat. de physiol.*, 1904-5, ii. 281.
15. Fredericq, *Ibid.*, 1906-7, v. 1.
16. von Frey, *Die Untersuchung des Pulses*, Berlin, 1892.
17. Gaskell, *Schäfer's Textbook of Physiology*, Edin. and Lond., 1900, ii. 179.
18. Gerhardt, *Arch. f. exper. Path. u. Pharmac.*, Leipz., 1902, xlvii. 250.
19. Gibson, A. G., *Lancet*, Lond., 1907, ii. 1380.
20. Gibson, A. G., *Quart. Journ. Med.*, Oxford, 1907-8, i. 173.
21. Gibson, G. A., and Ritchie, *Practitioner*, Lond., 1907, lxxviii. 589.
22. Hay, *Graphic Methods in Heart Disease*, Lond., 1909, 141.
23. Hay, *Ibid.*, 169.
24. Henschen, *Mitteil. a. d. med. Klinik zu Upsala*, 1898, i. (Quoted by Merklen.)
25. Hering, *Arch. f. d. ges. Physiol.*, Bonn, 1900, lxxxii. 1.
26. Hering, *Deutsch. Arch. f. klin. Med.*, 1904, lxxix. 175.
27. Hering, *Verhandl. d. 23. Kongr. f. inn. Med.*, Wiesbaden, 1906, 138.
28. Hering, *Deutsch. med. Woch.*, 1908, xxxiv. 638.
29. Hertz and Goodhart, *Quart. Journ. Med.*, Oxford, 1908-9, ii. 213.
30. Hirschfelder, *Bull. Johns Hopkins Hosp.*, Baltimore, 1907, xviii. 265.
31. Hirschfelder, *Ibid.*, 1908, xix. 322.
32. Huchard, *Journ. des praticiens*, 1892, vi. 417; *Maladies du Cœur: Artériosclérose*, Paris, 1910, 204, 205.
33. Joachim, *Deutsch. Arch. f. klin. Med.*, 1906, lxxxv. 373.
34. Jolly and Ritchie, *Heart*, Lond., 1910.
35. Knoll, *Sitz. d. k. Akad. d. Wissen. Wien*, 1872, lxvi. (Math.-Naturwiss. Classe, 3. Abtheil.) 195.
36. Koch, *Berl. klin. Woch.*, 1910, xlvii. 1108.
37. Laslett, *Brit. Med. Journ.*, 1909, i. 996.
38. Lewis, *Quart. Journ. Med.*, Oxford, 1909-10, iii. 269.
39. Lewis, *Ibid.*, 1909-10, iii. 337.
40. Lewis, *Heart*, Lond., 1910, i. 262.
41. Lewis, *Ibid.*, 1910, i. 306.
42. Lewis and Mack, *Quart. Journ. Med.*, Oxford, 1909-10, iii. 273.
43. von Leyden, *Virchow's Arch. f. path. Anat.*, Berlin, 1868, xlv. 365; *Deutsch. med. Woch.*, 1903, xxix. 361.
44. Lorain, *Études de médecine clinique: le pouls*, Paris, 1870, 341.

45. Mackenzie, *The Study of the Pulse*, Edin. and Lond., 1902, Fig. 93.
46. Mackenzie, *Ibid.*, Figs. 281, 282, 283.
47. Mackenzie, *Ibid.*, Figs. 320, 321.
48. Mackenzie, *Brit. Med. Journ.*, 1905, i. 521, 588.
49. Mackenzie, *Ibid.*, 759.
50. Mackenzie, *Amer. Journ. Med. Sci.*, 1907, cxxxiv. 12.
51. Mackenzie, *Quart. Journ. Med.*, Oxford, 1908, i. 131.
52. Mackenzie, *Ibid.*, 1908, i. 481, Fig. 12.
53. Mackenzie, *Ibid.*, 1908, i. 481, Fig. 13.
54. Mackenzie, *Heart*, Lond., 1909, i. 23.
55. Mackenzie, *Diseases of the Heart*, Lond., Second Edit., 1910, Figs. 115, 116, 117.
56. Mackenzie, *Ibid.*, chap. xxxiv, and Appendix VI.
57. Merklen, *Leçons sur les troubles fonctionnels du cœur*, Paris, 1908.
58. Mönckeberg, *Untersuchungen über das Atrioventrikulärbündel im menschlichen Herzen*, Jena, 1908.
59. Nicolai and Plesch, *Deutsch. med. Woch.*, 1909, xxxv. 2252.
60. Norris, *Univ. of Pennsylv. Med. Bnll.*, 1910, xxii. 342.
61. Piersol, *Amer. Journ. Med. Sci.*, 1908, cxxxv. 812.
62. Platnew, *Zeitschr. f. exp. Path. u. Therap.*, 1907, iv. 321.
63. Rautenberg, *Samml. klin. Vorträge*, 1909; 'Inn. Med.,' N. F. 171, 172, S. 91.
64. Rehfiach, *Deutsch. med. Woch.*, 1910, xxxvi. 1035.
65. Riegel, *Ibid.*, 1903, xxix. 795.
66. Rihl, *Zeitschr. f. exp. Path. u. Therap.*, 1906, iii. 274.
67. Ritchie, *Proc. Roy. Soc. Edinburgh*, 1904-5, xxv. 1085.
68. Ritchie, *Scot. Med. and Surg. Journ.*, 1907, xx. 509.
69. Robinson and Draper, *Arch. of Inter. Med.*, 1910, v. 168.
70. Rothberger and Winterberg, *Wien. klin. Woch.*, 1909, xxii. 839.
71. Schatilloff, *Zeitschr. f. klin. Med.*, 1899, xxxvii. 109.
72. Strubell, *Verhandl. d. 26. Kongr. f. inn. Med.*, Wiesbaden, 1909, Tafel XV, 11.
73. Traube, *Berl. klin. Woch.*, 1872, ix. 185.
74. Trendelenburg, *Arch. f. Anat. u. Physiol. (Physiol. Abt.)*, 1903, 271.
75. Unverricht, *Berl. klin. Woch.*, 1890, xxvii. 361.
76. Vinnis, *De aanhoudende Verdubbeling van den Hartslag: Hart-Bigeminie*, Proefschrift, Leiden, 1905.
77. Volhard, *Münch. med. Woch.*, 1905, lii. 590.
78. Wenckebach, *Die Arrhythmie als Ausdruck bestimmter Funktionsstörungen des Herzens*, Leipzig, 1903, 38, Fig. 7.
79. Wenckebach, *Ibid.*, 67-83.
80. Wenckebach, *Ibid.*, 160.
81. Wenckebach, *Ibid.*, Tafel VII, Figs. 36, 38, 41.
82. Wenckebach, *Arch. f. Anat. u. Physiol. (Physiol. Abt.)*, 1906, 297.
83. Wenckebach, *Ibid.*, 1908, Suppl. 53.
84. Wenckebach, *Ibid.*, 1908, Suppl., Figs. 5 a and 6 a.
85. Wardrop Griffith and Cohn, *Quart. Journ. Med.*, Oxford, 1909-10, iii. 126.

## DESCRIPTION OF FIGURES.

FIG. 1. Jugulo-carotid and radial tracings from a case of *pulsus alternans*. The time-record indicates 0.1 of a second (p. 58).

FIG. 2. Each extra-systole is followed by an alternating pulse in which the smaller arterial pulse wave is delayed. The time-record is 0.2 second. The apical tracing is an inverted cardiogram (p. 58).

FIG. 3. Case I. Jugulo-carotid and radial tracings, and diagram constructed therefrom. The intervals  $a-a$ ,  $a-c$ , and  $c-c$  are indicated in the diagram. There is a coupled rhythm of the ventricles in partial (3:2) auriculo-ventricular heart-block. The time-record indicates 0.1 of a second (p. 59).

FIG. 4. Brachial and apical tracings from a case of mitral stenosis and perpetual arrhythmia. The first beat after a long pause is followed by a premature beat. The time-record is 0.1 second (p. 80).

FIG. 5. Case II. Group-beating of the ventricles (p. 61).

FIG. 6. Case II. Group-beating of the ventricles associated with flutter of the auricles at a rate of 276.9 per minute (p. 61).

FIG. 7. Case III. Coupled rhythm with perpetual arrhythmia of the ventricles (p. 62).

FIG. 8. Case IV. Coupled rhythm with perpetual arrhythmia of the ventricles (p. 62).

FIG. 9. Case V. Occasional coupled beats of the ventricles. The second beat of each couple is a ventricular extra-systole (p. 64).

FIG. 10. Case VII. Coupled rhythm of the ventricles. The second beat of each couple is a ventricular extra-systole (p. 66).

FIG. 11. Case VII. Coupled rhythm of the ventricles, the second beat of each couple being a ventricular extra-systole. The auricles beat almost rhythmically throughout. The wave  $b$  is discussed on p. 66.

FIG. 12. Case VII. Tracings taken seven days later than those in Fig. 11. The coupled rhythm has disappeared. The  $a-c$  interval is 0.06 of a second (pp. 66, 69).

FIG. 13. Case VI. Coupled rhythm of the ventricles, a ventricular extra-systole occurring after each physiological beat (p. 64).

FIG. 14. Case VIII. Coupled rhythm of auricle and ventricle. The second beat of each couple is a 'nodal' extra-systole (p. 67).

FIG. 15. Case IX. The ventricles contract rhythmically after the disappearance of the coupled rhythm (p. 68).

FIG. 16. Case IX. Continuous coupled rhythm. The second beat of each couple, 2, is so premature that it is not represented in the brachial tracing (p. 68).

FIG. 17. Auriculo-ventricular heart-block. The third ventricular systole coincides with an auricular systole, and is quickly followed by a second contraction (p. 75).

FIG. 18. Case X, showing coupled rhythm and groups of three beats (p. 72).

FIG. 19. Case X, showing the termination of the coupled rhythm. The pause after the second beat of each couple is fully compensatory (p. 72).

FIG. 20. Case X. Regular rhythm (p. 71).

FIG. 21. Case X. Coupled rhythm of auricles and ventricles, both beats of each couple being due to stimuli from the same part of the heart. The tracing shows the onset of the coupled rhythm (p. 72). The time-record is 0.1 second.

FIG. 22. Case X, showing coupled rhythm (p. 72).

FIG. 23. Mitral endocarditis and partial heart-block. The short  $a-a$  intervals follow an auricular contraction occurring during ventricular systole. When the auricular and ventricular systoles coincided, the systolic murmur was much shorter and less loud than when the auricles contracted during ventricular diastole (p. 78). The time-record is 0.1 second.

FIG. 24. Each synchronous contraction of auricle and ventricle, occasioned by a ventricular extra-systole, is followed by an auricular extra-systole (p. 77).

FIG. 25. Case II. Coupled beats in auriculo-ventricular heart-block (p. 60).

FIG. 26. Case IX. The frequent beats of the brachial pulse correspond to rhythmic ventricular beats; the infrequent beats of the pulse were associated with a coupled rhythm of the ventricles. The second beat of each couple is represented in the cardiogram (Fig. 16) but not in the sphygmogram (p. 68).

FIG. 27. Respiratory and radial curves from a case of acute rheumatism. When the breathing is infrequent, there are groups of two or three pulse-beats separated by a long pause. With more frequent breathing, the pulse becomes accelerated and the irregularity lessened. The time-record is 0.1 second (p. 79).

FIG. 28. Brachial pulse tracing and time-record 0.2 second. The first beat after each unduly long diastole is followed by an extra-systole with a post-extra-systolic pause which is not fully compensatory (p. 80).

FIG. 29. Diagrams constructed from electro-cardiograms to show the contractions of auricle and ventricle in a case of mitral disease and heart-block. When auricular systole coincides with the beginning of ventricular systole, the latter is followed by a ventricular extra-systole (p. 76).

FIG. 30. Diagram to illustrate a prolonged diastole followed by a coupled rhythm of auricles and ventricles, the second beat of each couple being an extra-systole which originates in the auricle (p. 81).

FIG. 31. Diagram to illustrate a prolonged diastole followed by a coupled rhythm of the ventricles, the second beat of each couple being a ventricular extra-systole (p. 81).

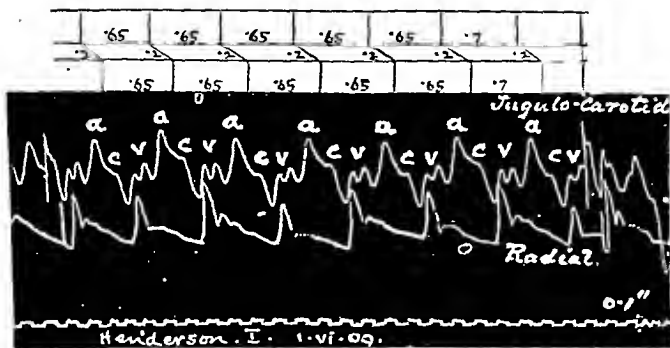


FIG. 1

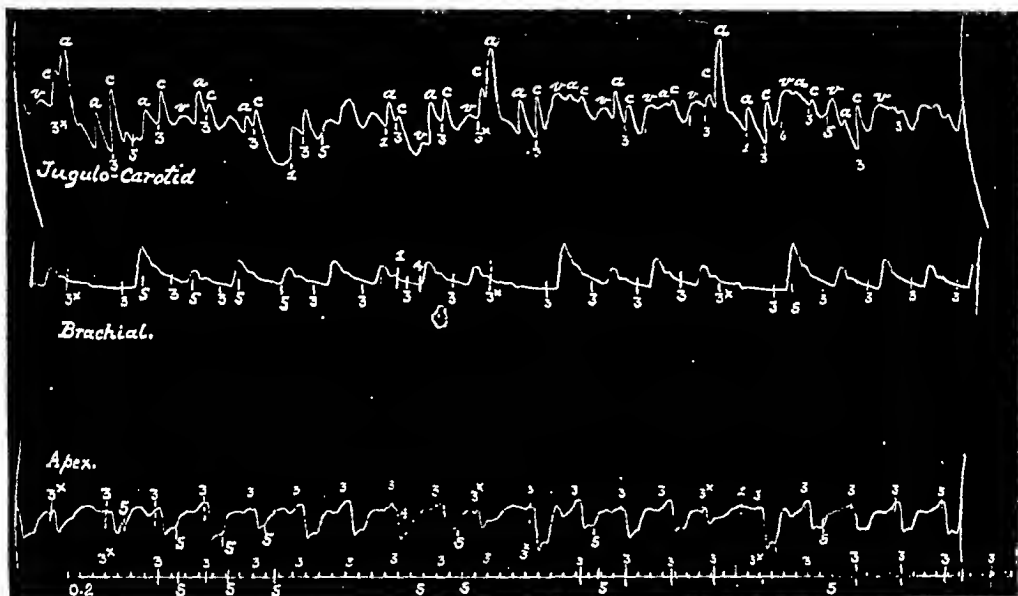


FIG. 2

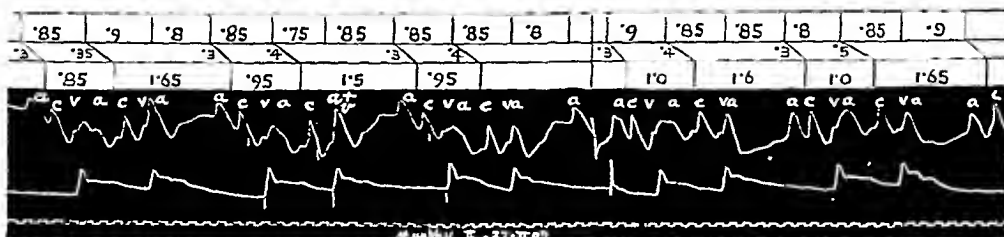


FIG. 3

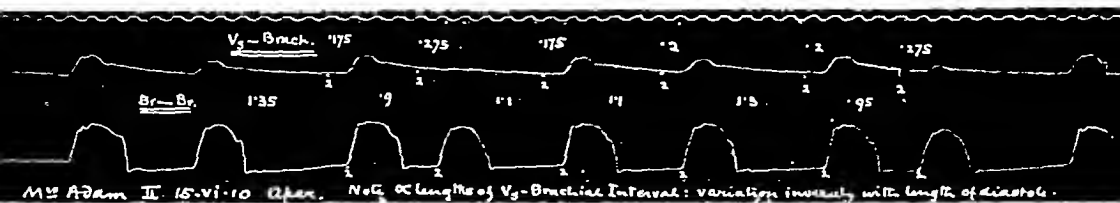


FIG. 4











FIG. 7

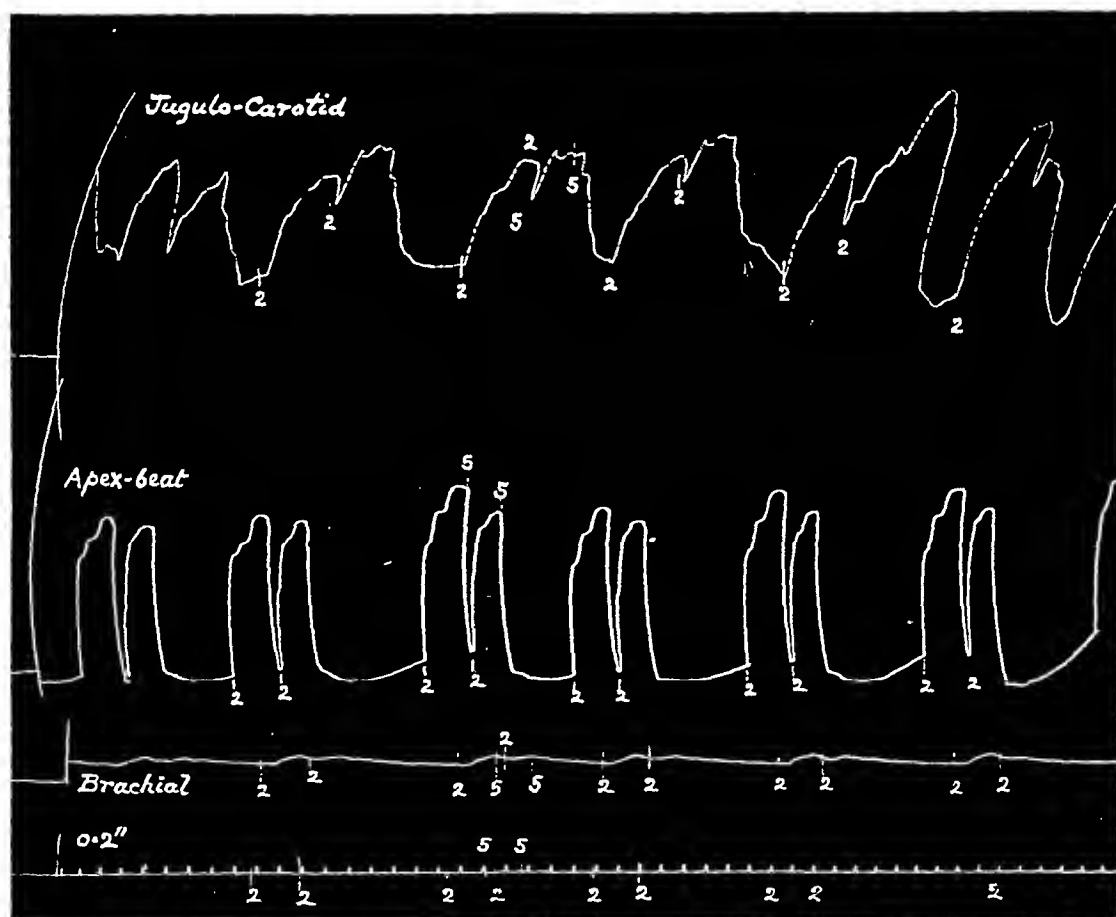


FIG. 8



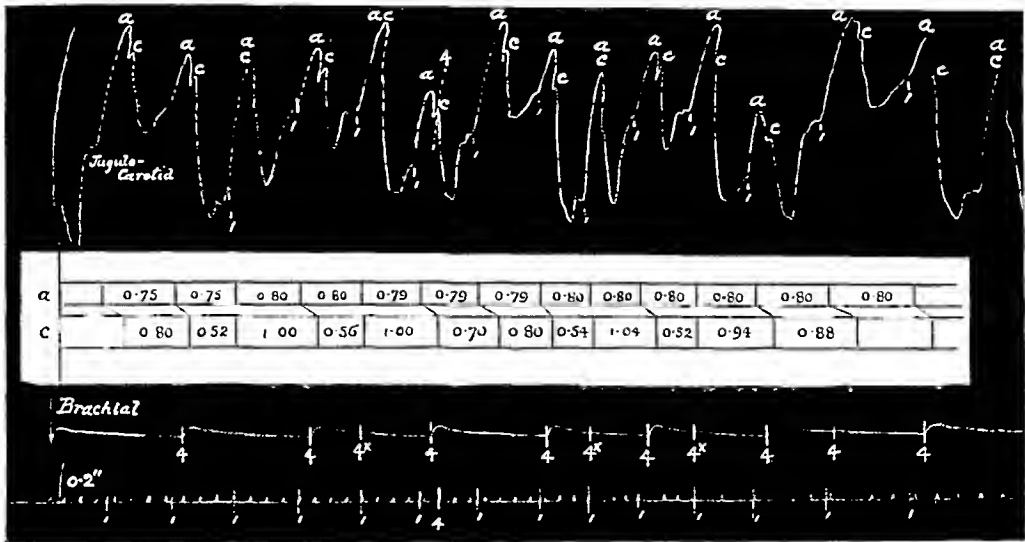


FIG. 9

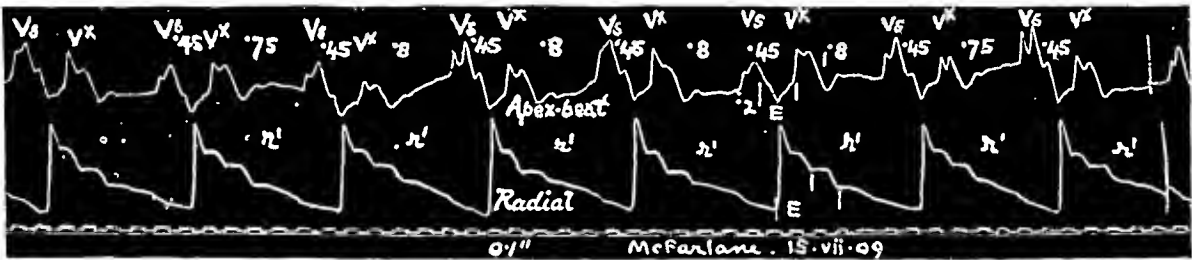


FIG. 10

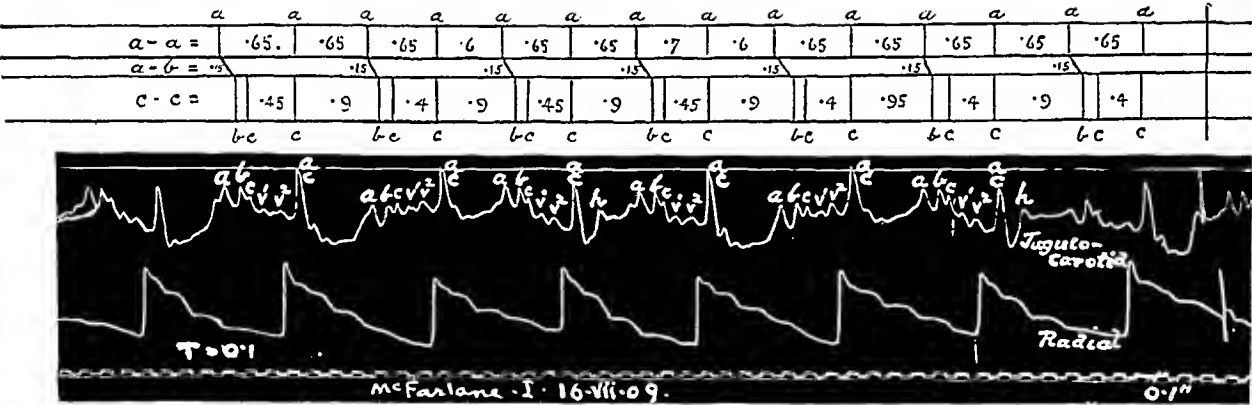


FIG. 11

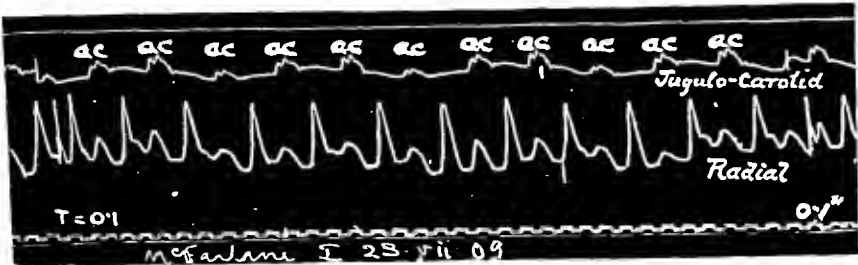


FIG. 12



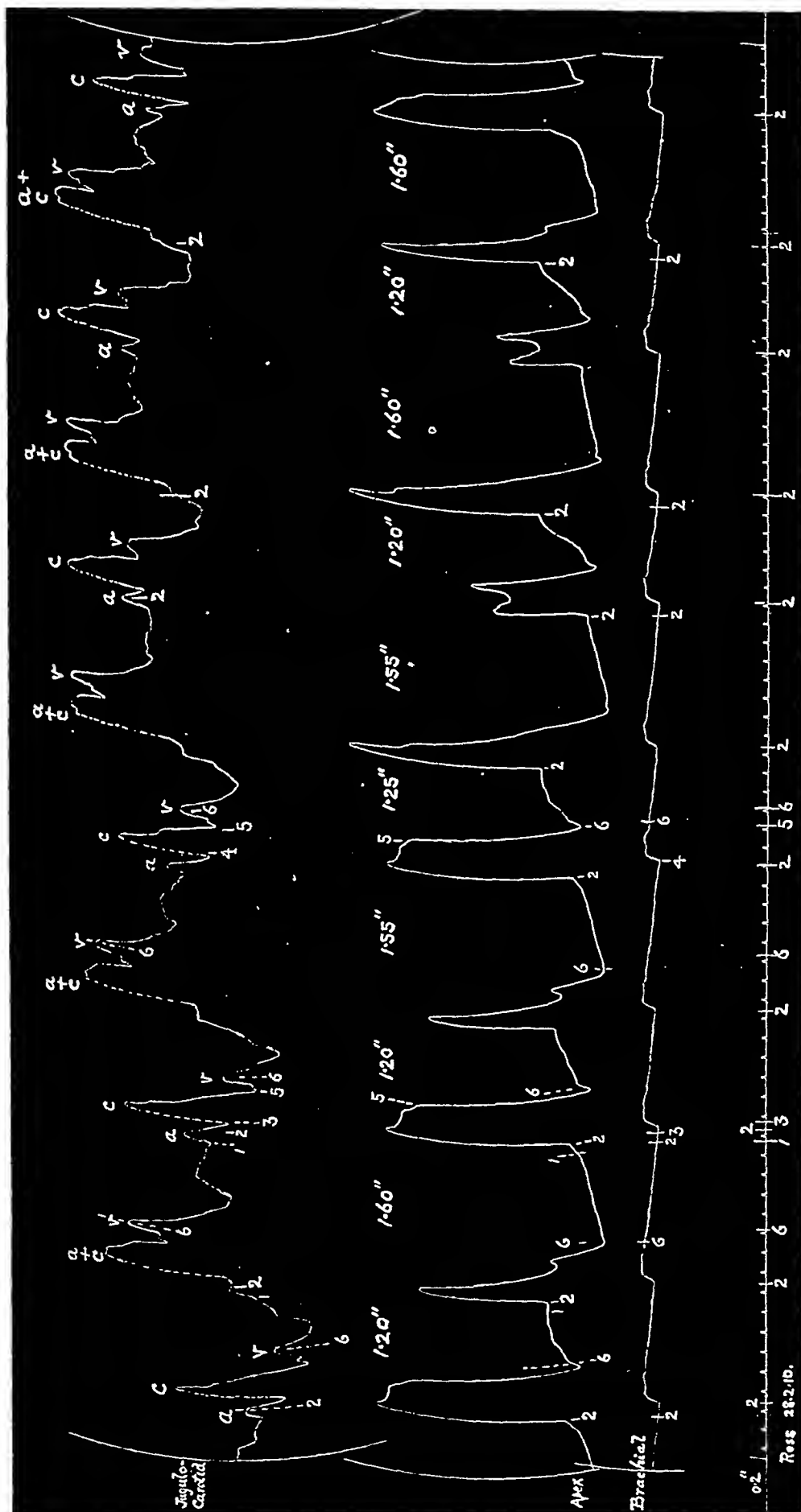


FIG. 13





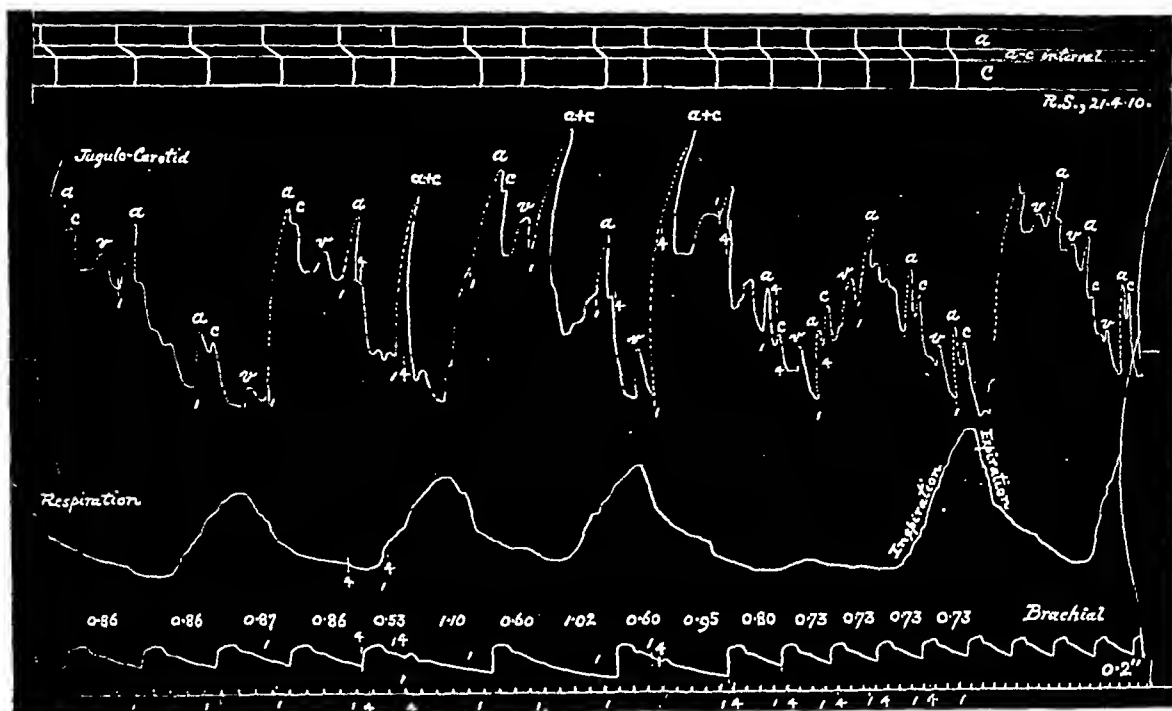


FIG. 14



FIG. 15



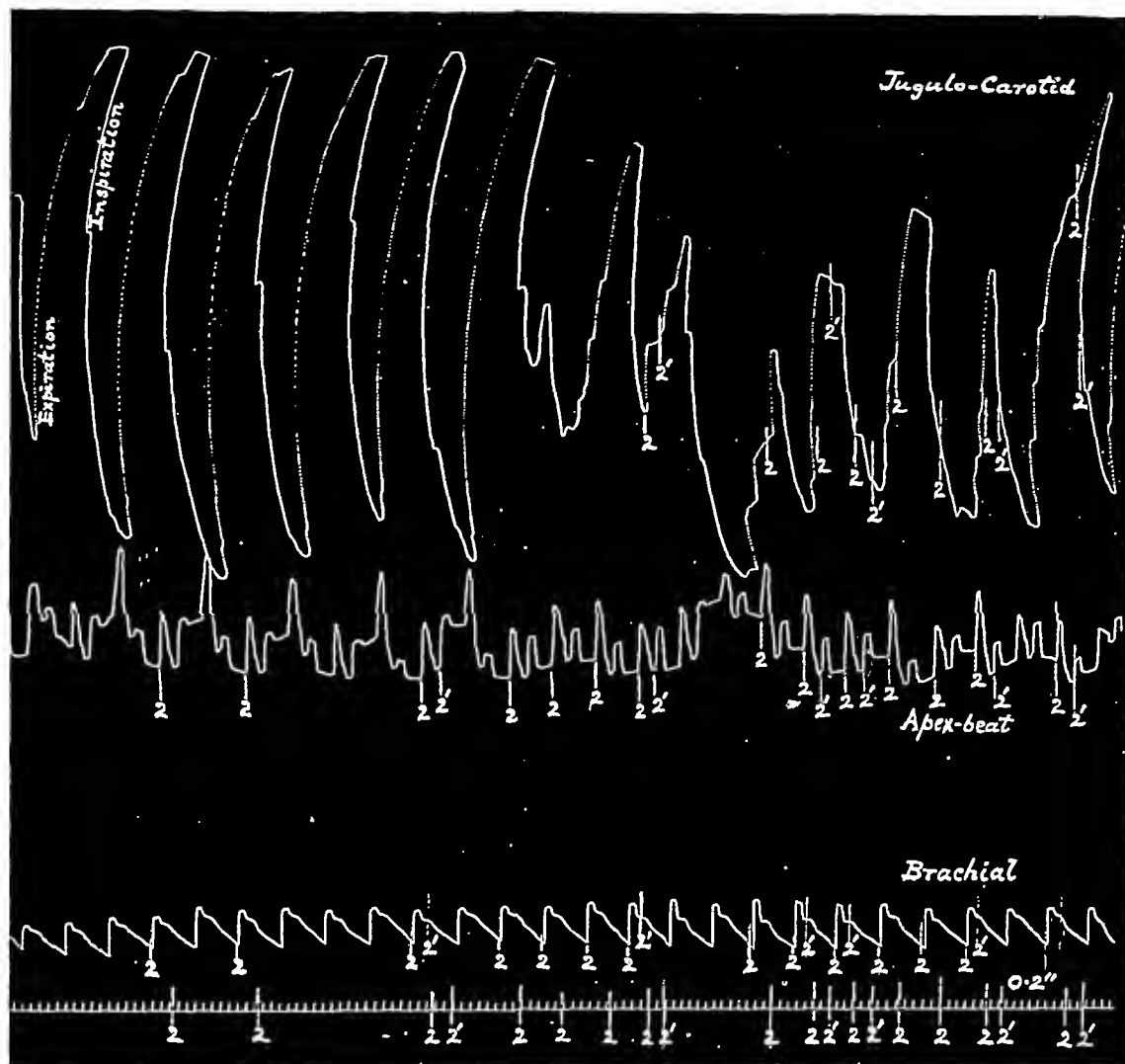


FIG. 16



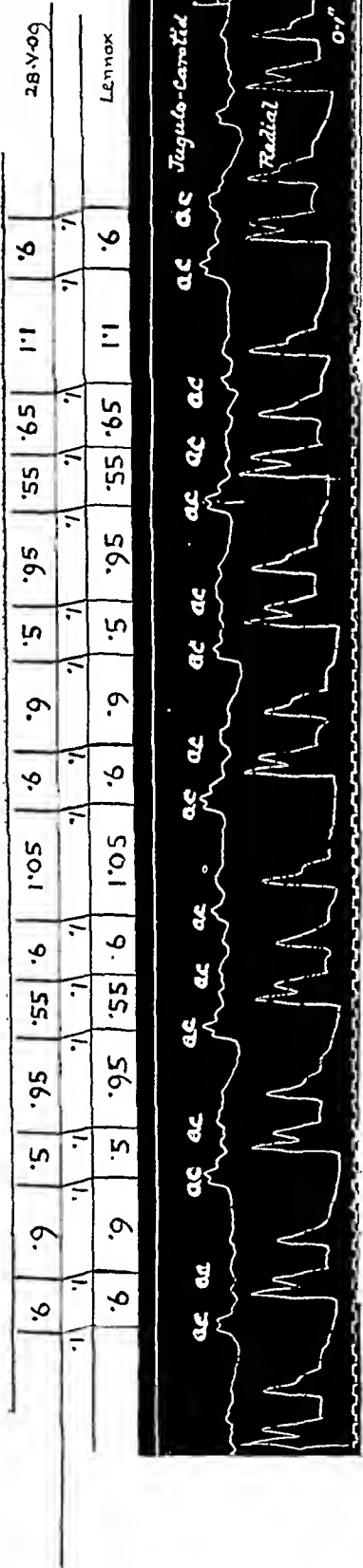


Fig. 18.

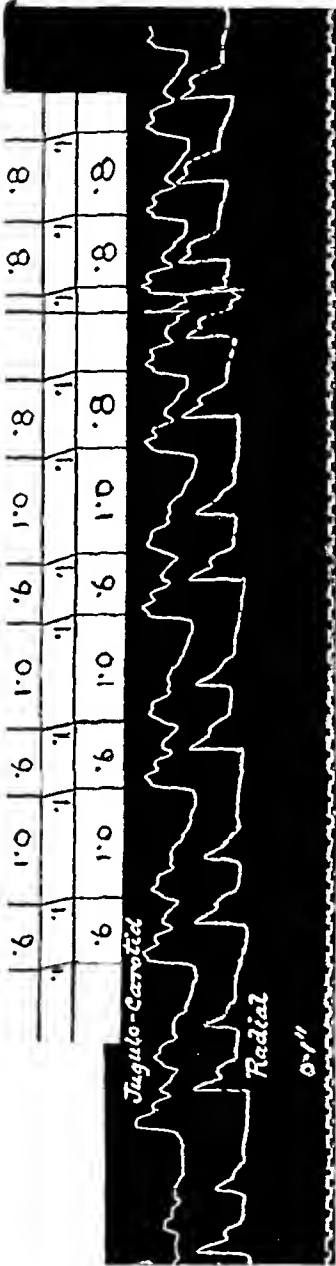


Fig. 19

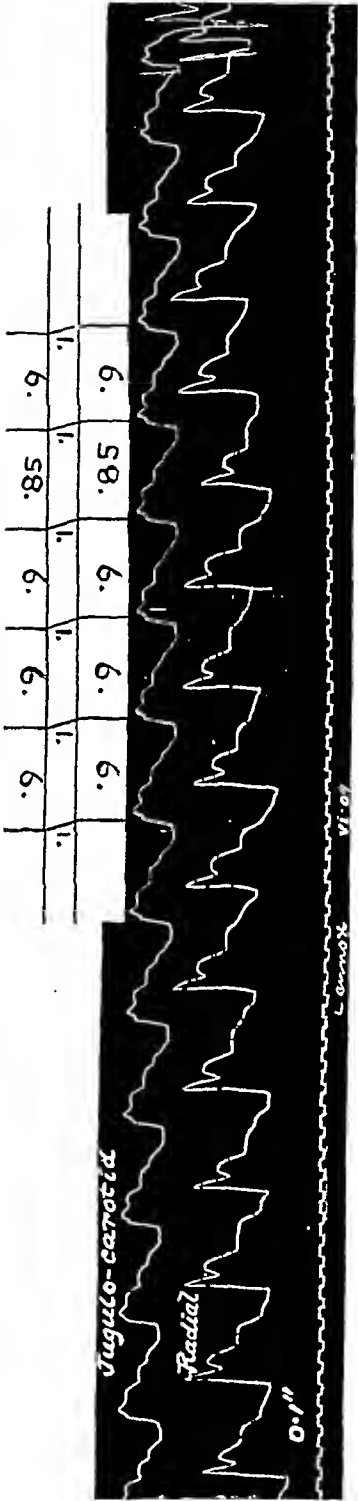


Fig. 20





**Fig. 21**

A	.5	1.0	.55	.95	.55	.95	.6	1.0	.5	1.0
C	.5	1.0	.55	.95	.55	.95	.6	1.0	.5	1.0

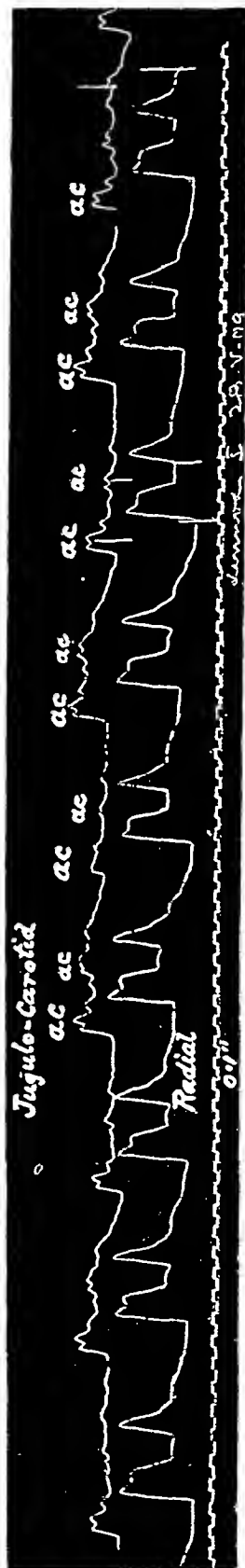


Fig. 22

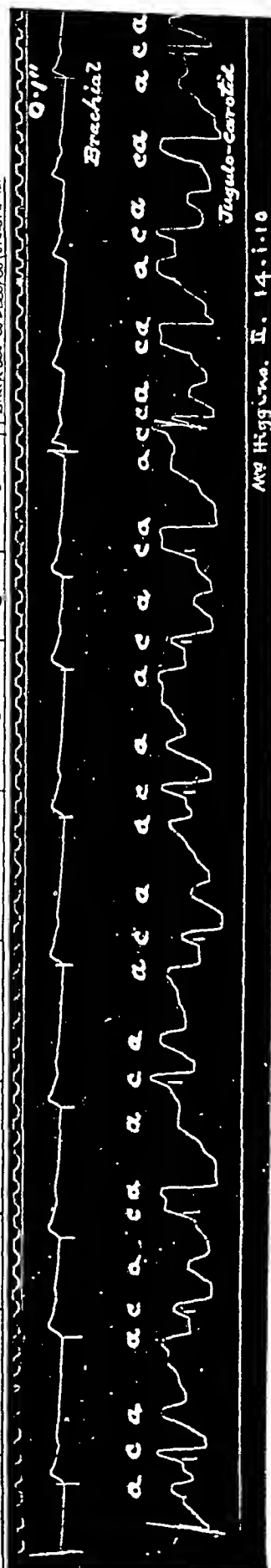
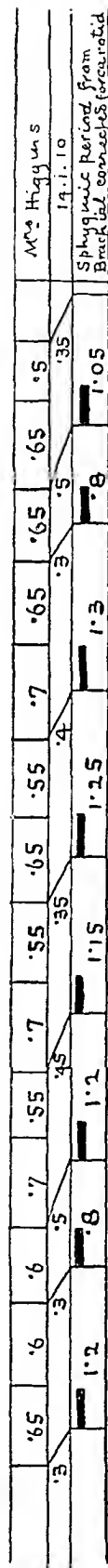


Fig. 23





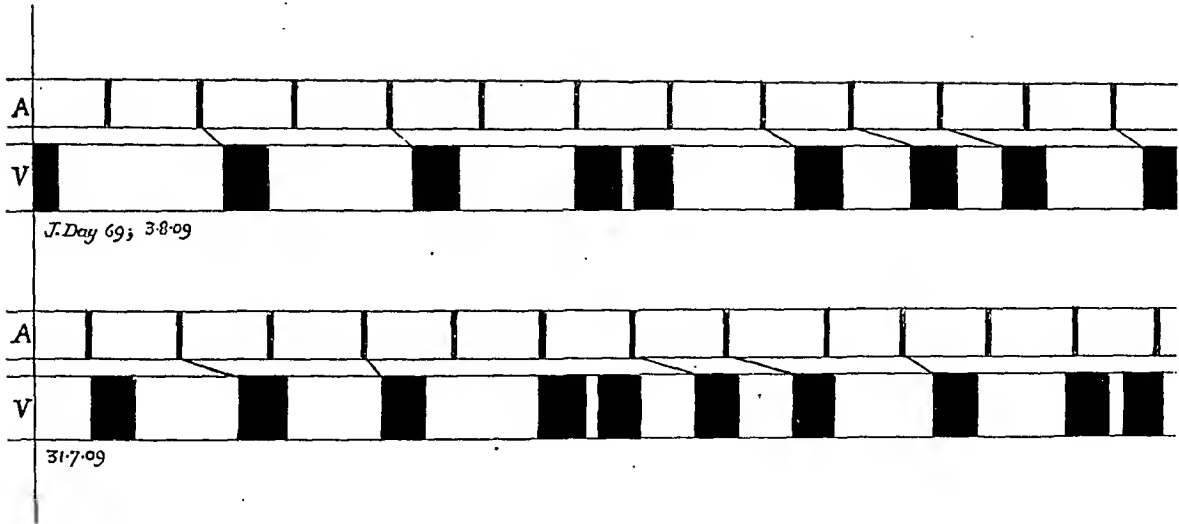


FIG. 29

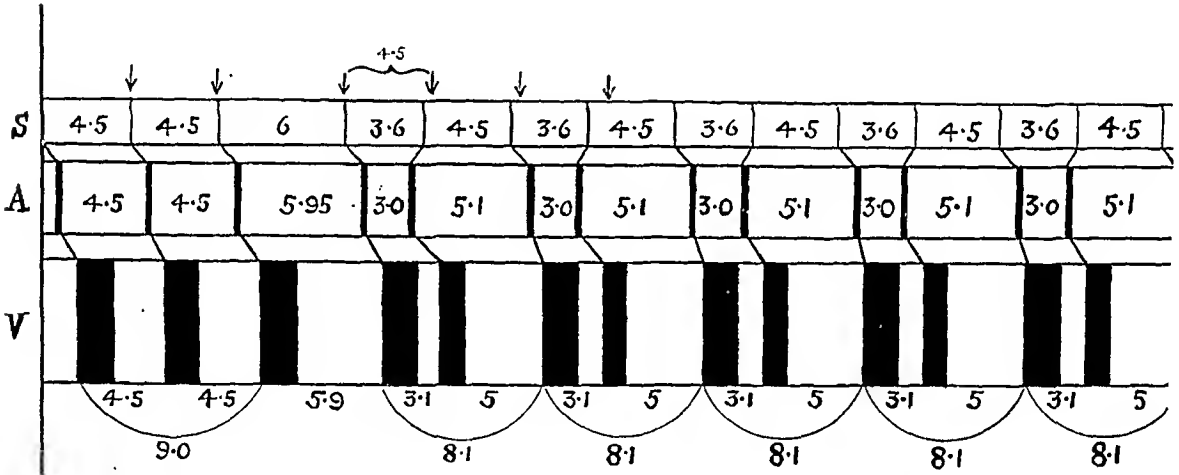


FIG. 30

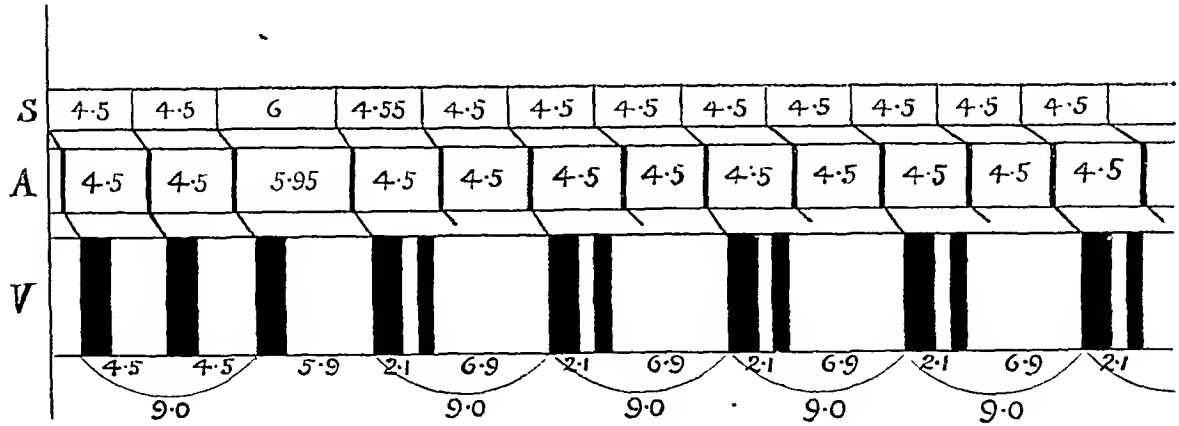


FIG. 31



# THE OUTLOOK OF SUFFERERS FROM EXOPHTHALMIC GOITRE

By W. HALE WHITE

THERE is much uncertainty as to whether it is desirable to operate for exophthalmic goitre, and doing so has frequently led to the death of the patient, therefore it seemed worth while to try to form some opinion as to the outlook for sufferers from this disease. In this paper the attempt has been made to do this by following the after-history of a large number of cases. I am much indebted to my Clinical Assistant, Dr. Jan Mahomed, for kindly writing to all the hospital patients, and to my colleagues for allowing me to refer to cases under their care. The hospital patients are those—169 in number—admitted into Guy's Hospital during the years 1888–1907 (both inclusive). I did not take those earlier than 1888, for very few who were in the hospital before 1888 can now be traced. Of the 169 cases

21 died in the hospital,  
54 can be traced,  

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75 accounted for,

leaving 94; the letters sent to 59 of these were returned 'Not known', the addresses of 5 were unintelligible, and 30 did not reply, although each was written to three times. The attempt was made in the spring of 1910 to find out what had become of every private patient suffering from exophthalmic goitre whom I had seen between 1894 and the end of 1909. In nearly every instance I was able to obtain information, and I should like to take this opportunity of thanking the many doctors who have answered my letters.

Reserving patients who have been operated upon for later consideration, my material from which to try to glean some information as to the outlook of sufferers from exophthalmic goitre who have not undergone any operation for this disease is that I have been able now (1910) to trace 49 patients (see Table A, which contains 54 cases, but 5, viz. 41, 45, 50, 52, 53, have been operated upon) who have been in Guy's Hospital during the twenty years 1888–1907 inclusive, and 53 private patients first seen between the years 1894 and 1909 inclusive (Table B of 57 private patients contains two, viz. 11 and 12, who could not be traced; they are included because they are mother and daughter and the past history showed the course of the disease; one, 53, who had one lobe of the thyroid

removed, and one, 57, who died while undergoing the same operation).<sup>1</sup> Among the 49 hospital patients 8 are now dead (Nos. 3, 5, 8, 10, 12, 14, 17, 33), and among the 53 private patients 7 are now dead (Nos. 3, 19, 27, 33, 45, 47, 52). I submitted my figures to my friend Mr. H. C. Thiselton and he has kindly given me an actuarial report, which is as follows :—

Group of hospital cases (Table A).

Owing to the paucity of the data it was impossible to deduce a column of the 'rate of mortality' which would be in any way reliable; and the only means of getting a very general idea of the mortality was to compare the actual deaths with those which would have occurred among the same body of lives if the mortality had followed that of a standard mortality table.

A comparison of the actual deaths was accordingly made with the 'expected deaths' according to the 'Healthy Females Experience of twenty British Offices amongst Assured Lives' (1863)—H<sup>f</sup>.

This comparison showed that the *total* number of deaths was approximately as under :—

- 8 actual deaths,
- 5 according to the H<sup>f</sup> Experience.

In view of the fact, however, that there were no known deaths at all over age 45, and only one death under age 30, it is quite impossible to draw any conclusions as to the comparative rates of mortality at the older and younger ages.

If we compare the mortality *between ages 30 and 45*, excluding two cases in which the age at death is unknown, we find that the number of deaths was as under :—

- 5 actual deaths,
- 3 according to the H<sup>f</sup> Experience.

Group of private cases (Table B).

In this second group a similar comparison was made, with the result that the mortality would seem to be very similar to that in the case of the first group.

The actual *total* number of deaths was as under :—

- 7 actual deaths,
- 3 according to the H<sup>f</sup> Experience.

In this case there was only one death over age 45 and two under 30. Comparing, as before, the mortality *between ages 30 and 45*, and excluding one death where the age at death is unknown, the number of deaths was as under :—

- 3 actual deaths,
- 2 according to the H<sup>f</sup> Experience.

As mentioned above, the data are so few that it would be dangerous to draw

<sup>1</sup> It also contains two other cases operated on, but in one, No. 54, all that was done was that the isthmus was divided to relieve dyspnoea, and the other, No. 21, had had one lobe removed seven years before, was as bad as ever when I saw her, and no operation was done for the condition for which I saw her. They are therefore included in the 53 cases.

any conclusions from the facts here set out, except perhaps the general conclusion that the mortality experience seems to be heavier than would be expected according to a well-known standard table.

I am sorry my cases are not sufficiently numerous to give more precise results, but I hope that others will add their collections of cases to the 102 (49 from Table A + 53 from Table B) here considered. The total deaths were 15, but the expected deaths according to the 'Healthy Females Experience Table' should have been 8. These figures suggest that if it were possible to obtain a great many more cases we should probably be able to prove that the expected mortality of sufferers from exophthalmic goitre not operated upon who have been in a hospital and discharged, and of sufferers from it in private practice who sought a second opinion (for all the private cases were referred to me by their usual medical attendant), would be about twice as great as it should be; but it must be remembered that nearly all the patients were of such an age that the expected deaths among the healthy are few, and therefore twice the expected number is not a great number. But this suggestion must not be transferred without qualification to exophthalmic goitre generally, because all the patients here considered were ill enough either to come into a hospital or to desire a second opinion. The inclusion of all cases of exophthalmic goitre, and therefore of many slight cases, would almost certainly make the expectancy of life better than appears from my figures. But, on the other hand, during the twenty years 1888-1907 18 sufferers from the disease died in the hospital (Table C of fatal hospital cases contains 21, but 3 died as a result of operation on the thyroid), therefore the total number of hospital cases (apart from those operated upon) of which we know the result up to date is  $49 + 18 = 67$ , of whom  $8 + 18 = 26$  are dead. This, however, gives too serious a view of the mortality, for during the twenty years under consideration there were 94 cases not operated upon who left the hospital and cannot be traced. If the mortality among them was the same as among the 49 who could be traced 15 would now be dead, giving a total mortality of  $26 + 15 = 41$  out of  $67 + 94 = 161$  hospital cases. These figures indicate that the outlook is more serious among the poor than among the well-to-do, for among 53 private patients only 7 died, and I shall later suggest a cause for this difference. I placed those who died in the hospital separately from those who could be traced from it, for all those who died in the hospital, apart from those who died as a result of an operation on the thyroid, were so ill that no operation on the thyroid gland could have been performed upon them, and I wished to see what became of those who left the hospital, so as to provide figures which might in the future be of use in determining whether an operation was desirable for those who were not so ill that it was impossible to operate upon them.

The fatal cases other than those operated upon need not detain us long. We will first consider those patients who died in the hospital (Table C). It is well known that diarrhoea and, to a less extent, vomiting often accompany exophthalmic goitre, and that in many instances these symptoms subside under

treatment, but one or both of these were very evident in 11 (1, 2, 3, 8, 10, 11, 12, 15, 16, 18, 19) of the 18 patients not operated on who died in the hospital during the twenty years under consideration, omitting one case in which the vomiting may have been due to cerebral softening (7). These figures indicate that it behoves us at once to put the sufferer from exophthalmic goitre to bed when vomiting or diarrhoea supervene, and to do our best to stop these symptoms. Often there is naked-eye evidence of gastro-enteritis at the post-mortem examination, and often, as was pointed out many years ago, Peyer's patches are prominent. It will be of interest in future cases to try to discover the micro-organism responsible for the gastro-enteritis, for it may then be possible to do good with a vaccine. Six cases (8, 9, 10, 11, 12, 15) became delirious and one (17) became comatose. I have no reliable figures to show how many who become delirious or comatose recover, but my impression is that the supervention of either is of bad augury. Two cases (12 and 16) had melancholia, and one (14) had mania. In one case (4) mitral disease was present and in one (10) endocarditis and pericarditis were present. Two (6, 10) had rheumatic fever and one (9) attributed the onset of the disease to rheumatic fever. These cases illustrate the well-known association between rheumatic fever and exophthalmic goitre. Two (11, 14) had pneumonia and one (15) broncho-pneumonia. One (13) apparently died of diabetic coma, a point of interest when we remember that glycosuria may be present in those who have exophthalmic goitre, but I know from observation that it may pass away and may not have returned twenty years after it was found. In only one of the 8 hospital patients who died outside the hospital was I able to find the cause of death; that patient died of pneumonia. Of the 7 private patients who died (apart from operation) one (3) succumbed to phthisis, one (27) to pleural effusion, one (52) to heart disease, one (33) to alcoholism, one (47) to diarrhoea, and two (19 and 45) to diabetes. Diarrhoea does not figure nearly so largely as among those who died in the hospital, and my impression is that it is more common among hospital than among private patients suffering from exophthalmic goitre. Probably this is due to the fact that private patients are much more likely than hospital patients to go to bed when they get diarrhoea, therefore it rarely becomes serious with them. We have already noticed the interest of death from diabetes. Considering the frequency with which cerebral symptoms (delirium, coma, melancholia, mania) occurred among the fatal hospital cases it is strange that they are not mentioned as having been present in any of the fatal private cases.

We will now see what is to be learnt from the cases which were traced and did not die. Let us first take the hospital cases (Table A) containing 54, of which 8 (3, 5, 8, 10, 12, 14, 17, 33) died. As all we know of No. 39 is that she is still alive, she cannot be considered, and Nos. 41, 45, 50, 52, 53 were operated on. Therefore  $8+1+5=14$  need not now be considered, leaving 40, which I have grouped into (a) those that have done well (1, 2, 4, 6, 9, 15, 18, 19, 20, 24, 25, 27, 28, 29, 30, 31, 32, 34, 35, 37, 40, 42, 47, 48, 49, 51), twenty-six in number, (b) those that are moderately well or simply describe themselves

as better (11, 13, 16, 21, 22, 26, 36, 38, 43, 44, 46, 54), twelve in number, and those (c) who are not well (7, 23), two in number.

With regard to group (a) a glance at the table will show that they really are very well. No. 1 has required no treatment since she left the hospital twenty-one years ago; 4 was a bad case in the hospital twenty years ago, has worked hard for eighteen years, has married, has three children, is now a widow; 6 in the hospital twenty years ago, since then worked as a district nurse, subsequently married, and has four children; 9, in the hospital sixteen years ago, feels quite well, has not had a doctor for twelve years; 15 when in the hospital eleven years ago had had the disease ten years, after leaving the hospital, since when she had had no treatment, she married, and has six children; 18, in the hospital eight and a half years ago, is now quite well, and has been in service for five years without a single day's illness; 24 is included in this group as she is able to go to work; 25 is working as a cook; 29 does not now know there is anything the matter; 32 is now quite well, and has been so since her discharge; 34 is 'wonderfully better'; 35 is perfectly well; 37 has had no return of old complaint and is married; 40, in the hospital eight and a quarter years ago, has been well ever since she left the hospital, went into service for four years, then married, has four children, and never needs a doctor 'although she pays into a club'; 47 was quite cured by an American goitre cure; 48 attributes her improvement to pregnancy. The other cases do not call for any special mention.

Turning to group (b) 11 is included in it as she has had several attacks of mental derangement, but she is now considerably better and in a situation; 13 says her health is fairly good but she was able to take a situation after leaving Guy's, then she married, and has two children; 16, 21, and 23 are now much better; 26 has a little breakdown occasionally but is much better on the whole; 36 is now much better; 38 has improved; 43, 44, 46, and 54 are all evidently, from the words they use, considerably better. These twelve cases have all improved, and no doubt some of them might with justice be put in group (a). Even the two cases which I have put in group (c), those not well, say that they are better. It seems therefore to be a fair conclusion to say that these 40 hospital cases have done well, and that judging by them exophthalmic goitre appears likely to get well even if no operation is performed, a conclusion borne out by clinical experience, for we do not often see elderly women suffering from it, and the mortality from it, which we have already discussed, is certainly not severe enough to account for this.

Now let us consider the private cases which did not die. Table B contains 57 cases, two (11 and 12) of which could not be followed after I saw them, but in both the history could be traced a long way back, so they may be included. From these 57 we must deduct 2 operated upon (53 and 57), and 7 (3, 19, 27, 33, 45, 47, 52) who died, leaving 48;<sup>2</sup> of these we know very little of No. 46, so we have 47 cases to consider. Grouping them in the same way as we did the hospital

<sup>2</sup> In a previous footnote I have stated why Nos. 21 and 54, although operated on, are not deducted.



treatment, but one or both of these were very evident in 11 (1, 2, 3, 8, 10, 11, 12, 15, 16, 18, 19) of the 18 patients not operated on who died in the hospital during the twenty years under consideration, omitting one case in which the vomiting may have been due to cerebral softening (7). These figures indicate that it behoves us at once to put the sufferer from exophthalmic goitre to bed when vomiting or diarrhoea supervene, and to do our best to stop these symptoms. Often there is naked-eye evidence of gastro-enteritis at the post-mortem examination, and often, as was pointed out many years ago, Peyer's patches are prominent. It will be of interest in future cases to try to discover the micro-organism responsible for the gastro-enteritis, for it may then be possible to do good with a vaccine. Six cases (8, 9, 10, 11, 12, 15) became delirious and one (17) became comatose. I have no reliable figures to show how many who become delirious or comatose recover, but my impression is that the supervention of either is of bad augury. Two cases (12 and 16) had melancholia, and one (14) had mania. In one case (4) mitral disease was present and in one (10) endocarditis and pericarditis were present. Two (6, 10) had rheumatic fever and one (9) attributed the onset of the disease to rheumatic fever. These cases illustrate the well-known association between rheumatic fever and exophthalmic goitre. Two (11, 14) had pneumonia and one (15) broncho-pneumonia. One (13) apparently died of diabetic coma, a point of interest when we remember that glycosuria may be present in those who have exophthalmic goitre, but I know from observation that it may pass away and may not have returned twenty years after it was found. In only one of the 8 hospital patients who died outside the hospital was I able to find the cause of death; that patient died of pneumonia. Of the 7 private patients who died (apart from operation) one (3) succumbed to phthisis, one (27) to pleural effusion, one (52) to heart disease, one (33) to alcoholism, one (47) to diarrhoea, and two (19 and 45) to diabetes. Diarrhoea does not figure nearly so largely as among those who died in the hospital, and my impression is that it is more common among hospital than among private patients suffering from exophthalmic goitre. Probably this is due to the fact that private patients are much more likely than hospital patients to go to bed when they get diarrhoea, therefore it rarely becomes serious with them. We have already noticed the interest of death from diabetes. Considering the frequency with which cerebral symptoms (delirium, coma, melancholia, mania) occurred among the fatal hospital cases it is strange that they are not mentioned as having been present in any of the fatal private cases.

We will now see what is to be learnt from the cases which were traced and did not die. Let us first take the hospital cases (Table A) containing 54, of which 8 (3, 5, 8, 10, 12, 14, 17, 33) died. As all we know of No. 39 is that she is still alive, she cannot be considered, and Nos. 41, 45, 50, 52, 53 were operated on. Therefore  $8 + 1 + 5 = 14$  need not now be considered, leaving 40, which I have grouped into (a) those that have done well (1, 2, 4, 6, 9, 15, 18, 19, 20, 24, 25, 27, 28, 29, 30, 31, 32, 34, 35, 37, 40, 42, 47, 48, 49, 51), twenty-six in number, (b) those that are moderately well or simply describe themselves



	Mild or average.	Severe.	Very severe.
9 Private . . .	1, 5, 11, 28, 32, 37, 38	2	54
	<hr/> 7	<hr/> 1	<hr/> 1
Cases that did not do well:			
2 Hospital . . .	7, 3	0	0
3 Private . . .	13, 38	16	0
	<hr/> 4	<hr/> 1	<hr/> 0

It is of interest to notice that 8 hospital and 17 private cases grouped as severe or very severe have done well. We have already seen that the mortality is higher among hospital than private cases. Therefore these figures indicate that at any rate for those severely ill the outlook is better the better the social position.

The tables at the end of this paper state how long each patient said she had been ill. I have not attempted to draw any conclusions from this, for the patient's statement may be unreliable, and the period in the illness at which the patient comes under observation depends upon the severity of the symptoms and other factors.

We will now consider the hospital cases which have been operated upon. Five (41, 45, 50, 52, and 53) are in Table A. 41 does not say what operation was performed, but as it was done in 1905 we may safely assume that one lobe of the thyroid was removed, she says she is better; 45 had the right lobe removed six years ago, now she is fairly well and better for the operation; 50 had the right lobe and isthmus removed, she 'received great benefit' but her health is now 'very bad at times'; 52 had right lobe removed and is now perfectly well; 53 had the left lobe removed, she is better but by no means well. All these five were mild or average cases, and in all three or more years have elapsed since the operation. Three hospital cases, none of them severe cases, died as an immediate result of operation, Table C (5, 20, 21); 5 died, as have many patients after removal of part of the thyroid, from nervous symptoms and pyrexia; 20 died the day after the removal of one lobe, and 21 died on the operation table while the inferior thyroid arteries were being tied. Of the private cases three were operated on (21, 53, 57); 54 is not included as only the isthmus was divided. No. 21, a severe case, had the left lobe removed, was better for a time, then the right lobe enlarged enormously and she had again all the symptoms of exophthalmic goitre to an extreme degree; 53, an average case, was certainly better after removal of the right lobe, but sixteen years after the report was 'Distinctly better, no exophthalmos, some tachycardia, and palpitation. Nervous symptoms much the same. Still odd mentally.' 57, a severe case, died on the operating table. Altogether my series contains 11 cases operated on—only 2 of them severe—and 4 died as a result of the operation,<sup>3</sup> one is perfectly well, the others are much better but not completely

<sup>3</sup> This is about the same proportion of deaths as given by Dr. Hector Mackenzie for the patients operated on at St. Thomas's Hospital, when he spoke during the debate on the surgical treatment of exophthalmic goitre held at the meeting of the British Medical Association, London, 1910.

cured. We saw that the total mortality of hospital cases not operated on might be put at 41 out of 161, and among 53 private cases 7 died, giving a total number of deaths of 48 out of the 214, or 1 in 4.5, so that the operation result of 4 deaths out of 11 cases gives a higher mortality, and it must be remembered that 48 deaths among those not operated upon include many (at least 18) who were so ill that no one would have dreamt of operating on them, and that the mortality of the cases operated on is a mortality as a result of the operation, death taking place at or very shortly after operation, so that as far as my series goes it appears to show that operation is undesirable, especially as the cure ascribed to it, when death did not occur, was usually not complete; indeed one case was a few years after as bad as ever. But in the hand of surgeons doing many operations on the thyroid the mortality has gradually been brought down to 4 per cent. (Kocher, Mayo) and rather over 70 per cent. of the patients operated on are said to be cured, and Kocher states that the mortality among his more recent operations is even less. These however are the most encouraging results. Krecke recently collected 188 operation cases from 5 Clinics, and found the mortality to be 9 per cent. But to get the best results after operation those patients are selected who have not had the disease long, who have no lesions of other organs and have no mental symptoms. We have seen that if we exclude patients who are so ill that they die while in the hospital (and therefore are quite unsuitable for operation), and follow for some years the patients who are discharged from the hospital and those who are seen in private practice, the actual deaths among sufferers from exophthalmic goitre, ill enough to go into the hospital or seek a second opinion, are 15 as against 8 expected among healthy females, although these patients afflicted with exophthalmic goitre include severe and very severe cases, those with other diseases in addition, and those with mental symptoms. As on the other hand the cases selected for operation are chosen mostly from among the mild cases and a few die as an immediate result of the operation, it hardly seems likely that operations on the thyroid can diminish greatly the deaths that might, if the patients were not operated upon, be expected among such sufferers from exophthalmic goitre as are likely to be selected as suitable for having operations performed on their thyroid. It is, however, quite possible that operation may hasten the cure; if so, the justification for doing it will be greater among wage-earners than among others. It would be of great interest if a large series of cases that have been operated on could be traced for many years after the operation, so that we might learn more about the rapidity of the improvement, the duration of it, and the number of deaths as contrasted with those that might be expected among a similar number of healthy females. This is particularly important, for if the thyroid which after operation consists of one lobe shrinks, it may be that this leads after years to a mild degree of symptoms due to insufficiency of thyroid secretion. At any rate the cases here tabulated show that many patients, even those severely ill, recover and remain well for years without any operation; and that those who decline operation can hardly be considered unreasonable, especially in this

country, where the mortality from such operations is higher than in some others. Further, we have to bear in mind that we may sometimes be in error in attributing benefit to an operation for exophthalmic goitre, for we shall see directly that some patients recover without any treatment and so some operated upon might have done well even if no operation had been performed.

A survey of the tables at the end of this paper shows that some patients get well even under most unfavourable circumstances. For example, Case 39, Table B, a poor woman, had the disease very severely, she could not rest, but she got quite well.

After each of the following cases in Table A, the number of days' stay in the hospital is placed: No. 4 (49), No. 9 (14), No. 15 (11), No. 18 (36), No. 19 (14), No. 26 (95), No. 27 (46), No. 30 (58), No. 34 (55), No. 35 (45), No. 49 (170), No. 51 (9). None of these patients improved during their stay in the hospital, often probably because of its shortness, but many stayed a long while without improvement; yet all of these patients ultimately got quite well or very nearly well some time after they left the hospital and are now well, although the mode of life of hospital patients outside the hospital is the reverse of that which might be expected to aid cure. Thus No. 4 got well, married, had three children, became a widow, and is now, twenty years after her discharge, working hard. No. 15 married, had six children, and has had no treatment since she left the hospital. No. 18 has been in service five years without a single illness. Only two of these, Nos. 26 and 30, are classified as severe. From these cases we must conclude that some patients recover from exophthalmic goitre without any treatment.

The treatments used have been so various, and it is so difficult to tell the duration of each, that it is impossible to draw any certain conclusions about any of them, but from my own experience of patients that I myself have seen, and reports of others that I have read, my strong impression is that the most important treatment is absolute rest in bed for weeks or months, with freedom from anxiety. Recently a woman came into the hospital suffering from exophthalmic goitre; while in the hospital she had an attack of typhoid fever, her exophthalmic goitre continued to improve and she got quite well: most likely the rest compelled by the typhoid fever contributed to the cure of the exophthalmic goitre. Probably it is because private patients are better able to rest than hospital patients that the outlook for the latter is more serious than for the former. Next to rest comes food; no patients do well if they lose weight, and those who are already thin will not improve until by abundant food they gain weight. If they are very nervous, excitable, or sleepless, it is necessary that they should be quieted and given sleep; for this bromides often suffice, but it may be necessary to use hyoscine. If the pulse is very rapid it is probably wise to give digitalis. I have often given Moebius' serum; it appears sometimes to do good, but the cases vary so that it is difficult to adduce proof of this. The anaemia usually passes away as the patient improves. Many of the women

who were cured bore children; this does not do them any harm and they stand confinements well. Patients who are once cured do not often relapse, hence readmissions are few (7 per cent.).

I do not claim that there is anything new in this paper, but I collected the cases because it is only by reviewing the course of a disease apart from operation that the desirability of operating can be decided.

## TABLE A.

## FIFTY-FOUR HOSPITAL CASES THAT CAN BE TRACED.

All or nearly all these rested during the greater part of their stay in the hospital.

1. F; age 41. Hospital 14 days. Symptoms first noticed 8 years before. Average case: Considerable palpitation. Last heard of after 21 years. Result: Improved in hospital. Now writes to say she 'is much better'. Has required no treatment since she left the hospital. Treatment: Guaiacum. Ref. no. 6.
2. F; age 28. Hospital 26 days. Symptoms first noticed 3 years before. Bad case: Much palpitation. P. 130. Very excitable. Had chorea. Last heard of after 21 years. Result: Slightly better in hospital. Now seen at hospital where she came to report herself 'much better'. Treatment: Digitalis. Ref. no. 7.
3. M; age 24. Hospital 18 days. Symptoms first noticed 4 months before. Moderate case. Last heard of after 20 years. Result: Slight improvement during his short stay. Only information obtainable is that he died 1909. Treatment: Galvanism. Ref. no. 12.
4. F; age 20. Hospital 49 days. Symptoms first noticed 1 year before. Much thyroid enlargement. Exophthalmos and tachycardia. P. 140. Last heard of after 20 years. Result: No better for stay in hospital. Seen 1910, says she is quite well, has had no special treatment. Has married, has 3 children, now a widow. Works hard and has done so for 18 years. Treatment: Bromides and belladonna. Ref. no. 17.
5. F; age 21. Hospital 31 days. Symptoms first noticed 1 year before. Severe case in all respects. Result: Died of pneumonia soon after leaving the hospital. Treatment: Galvanism. Ref. no. 19.
6. F; age 30. Hospital 55 days. Symptoms first noticed 1 year before. Average case except that she was very excitable. Last heard of after 18 years. Result: Slight improvement on discharge. Rested 4 months and was then able to work as district nurse. Seen 1910. No palpitation nor enlarged thyroid. Has married. Had 4 children. Eyes still slightly prominent but otherwise well, and has remained so since 6 months after leaving hospital. Treatment: Galvanism, belladonna, digitalis. Ref. no. 24.
7. F; age 24. Hospital 68 days. Symptoms first noticed 1 year before. Average case. Last heard of after 17 years. Result: Says she is better in some respects, worse in others. Treatment: Bromides and belladonna. Ref. no. 29.
8. F; age 27. Hospital 15 days. Symptoms first noticed 6 years before. Average case. Result: Died in 1904, cause unknown. Ref. no. 33.
9. F. Hospital 14 days. Symptoms first noticed 7 years before. Average case. P. 136. Apical systolic murmur. Last heard of after 16½ years. Result: Left the hospital in the same condition as on admission, but now writes: 'Feels quite well and has not had a doctor for 12 years.' Treatment: Electrical, belladonna, bromides. Ref. no. 35.
10. M; age 29. Hospital 13 days. Symptoms first noticed 10 weeks before. Average case. P. 108. Complains of weakness; systolic apical murmur. Result: Slight improvement on discharge. Died soon after leaving hospital, cause unknown. Treatment: Digitalis and belladonna. Ref. no. 42.
11. F; age 39. Hospital 63 days. Symptoms first noticed 9 months before. Average case. Systolic murmur audible at apex. Last heard of after 15½ years. Result: Improved in hospital. Now writes: 'Goitre much smaller, eyes less prominent, has had several attacks of prolonged severe mental derangement, but is now considerably better.' Is now in a situation. Treatment: Thyroid, belladonna, and digitalis. Ref. no. 44.
12. F; age 25. Hospital 4 days. Symptoms first noticed 1 year before. Slight case. Result: Only information obtainable is she died in 1905, cause unknown. Ref. no. 63.
13. F; age 21. Hospital 33 days. Symptoms first noticed 1 year before. Mild case. Last heard of after 11½ years. Result: Symptoms including tremors have disappeared. Not improved by stay in hospital. Took a situation a year after leaving hospital, then married, 2 children. Health fairly good. Treatment: Belladonna, digitalis. Ref. no. 67.
14. F; age 26. Hospital 9 days. Symptoms first noticed 1 year before. Average case. Last heard of after 11½ years. Result: Died after leaving hospital. Cause and date unknown. Ref. no. 69.
15. F; age 23. Hospital 11 days. Symptoms first noticed 10 years before. Average case. P. 120. Tremors. Last heard of after 11 years. Result: No better on discharge from hospital but improved soon after. Is married. Has six children. Has required no treatment for 11 years. Treatment: Adrenalin, arsenic, digitalis. Ref. no. 76.
16. F; age 23. Hospital 45 days. Symptoms first noticed 6 months before. Average case. Loss of weight a striking feature. Last heard of after 9½ years. Result: Was not so

- well when she left hospital as when she came in. Is now much better. Treatment: Adrenalin, digitalis, bromide. Ref. no. 79.
17. F; age 37. Hospital 97 days. Symptoms first noticed 1 year before. Severe case: P. 150. Delirium and vomiting. Result: Died in 1901. Cause unknown. Treatment: Cold to neck, electricity, massage. Ref. no. 82.
18. F; age 19. Hospital 36 days. Symptoms first noticed  $1\frac{1}{4}$  years before. Average case: Considerable anaemia. Last heard of after  $8\frac{1}{2}$  years. Result: Slight improvement on discharge. She is now quite well. Has been in service 5 years without a single day's illness. Treatment: Digitalis, belladonna. Ref. no. 85.
19. F; age 54. Hospital 14 days. Symptoms first noticed 6 years before. Average case: Very nervous, skin pigmented. Last heard of after  $7\frac{1}{4}$  years. Result: No improvement from stay in hospital, but is now very much better. Treatment: Thymus, belladonna, digitalis. Ref. no. 87.
20. F; age 36. Hospital 45 days. Symptoms first noticed 6 weeks before. Average case: P. 120. Tremors, apical systolic murmur. Last heard of after  $8\frac{1}{4}$  years. Result: Better on discharge. Says she is now quite well. Treatment: Belladonna, potassium iodide. Ref. no. 96.
21. F; age 28. Hospital 130 days. Symptoms first noticed 6 years before. Severe case: Much palpitation; wasting; mania. Last heard of after 7 years. Result: Better on discharge. Is now much better. Treatment: Belladonna, bromides. Ref. no. 99.
22. F; age 39. Hospital 24 days. Symptoms first noticed 6 months before. Mild case. Last heard of after 7 years. Result: Better on discharge. Is now better. Treatment: Digitalis, opium. Ref. no. 100.
23. F; age 34. Hospital 50 days. Mild case but had glycosuria and polyuria. Last heard of after  $7\frac{1}{2}$  years. Result: No improvement on discharge. Now throat not swollen, better in some respects. Palpitation better. Suffers from nerves. Complains much of dryness of mouth. Treatment: Opium, belladonna. Ref. no. 101.
24. F; age 30. Hospital 5 days. Symptoms first noticed 8 years before. Mild case. Last heard of after 6 years. Result: Now writes: 'About the same.' But is able to go to work. Ref. no. 104.
25. M; age 19. Hospital 3 days. Symptoms first noticed 6 months before. Average case. Last heard of after  $5\frac{1}{2}$  years. Result: Much better soon after leaving hospital, and has kept so. Has never had to give up work; is a cook. Treatment: Bromides, digitalis. Ref. no. 108.
26. F; age 34. Hospital 95 days. Symptoms first noticed 7 years before. Severe case: P. 140. Anaemia, wasting, pigmentation. Last heard of after  $6\frac{1}{2}$  years. Result: No improvement in hospital. Now 'has a little breakdown occasionally, but is much better on the whole'. Treatment: Belladonna. Ref. no. 109.
27. M; age 42. Hospital 46 days. Symptoms first noticed 2 months before. Mild case: Complained of weakness. Last heard of after  $5\frac{1}{4}$  years. Result: No improvement in hospital. Now seen at hospital, is much better, hardly any signs of the disease left. Treatment: Adrenalin, bromides. Ref. no. 112.
28. F; age 21. Hospital 80 days. Symptoms first noticed 6 years before. Average case: Some diarrhoea and vomiting. Last heard of after  $5\frac{1}{2}$  years. Result: Slightly better on discharge. Now 'very much better'. Treatment: Adrenalin, digitalis, belladonna, opium. Ref. no. 113.
29. F; age 28. Hospital 18 days. Symptoms first noticed 6 weeks before. Mild case. Last heard of after 5 years. Result: Better when discharged. Now 'does not know there is anything the matter'. Ref. no. 115.
30. F; age 20. Hospital 58 days. Symptoms first noticed 3 months before. Severe case: P. 140. Wasting, sweating. Last heard of after 5 years. Result: No improvement on discharge. Now 'very much better'. In a situation as lady's-maid. Treatment: Digitalis. Ref. no. 116.
31. F; age 40. Hospital 18 days. Symptoms first noticed 6 weeks before. Severe case: Weakness, diarrhoea, systolic murmur, pigment. Last heard of after 3 years. Result: Improved in hospital. When last heard of in 1909 was 'alive and well'. Ref. no. 117.
32. F; age 22. Hospital 29 days. Symptoms first noticed 3 months before. Mild case. Last heard of after 4 years. Result: Improved when discharged. Now 'quite well', and has been so since discharged. Treatment: Bromides, digitalis, belladonna. Ref. no. 119.
33. F; age 25. Hospital 47 days. Symptoms first noticed 1 year before. Average case. Result: Improved in hospital. Died since. Cause and date unknown. Treatment: Aspirin. Ref. no. 120.
34. F; age 42. Hospital 55 days. Symptoms first noticed 3 years before. Average case. Last heard of after  $4\frac{1}{4}$  years. Result: No improvement on discharge, but now 'wonderfully better'. Treatment: Potassium iodide. Ref. no. 121.
35. F; age 31. Hospital 45 days. Symptoms first noticed 5 weeks before. Slight case. Last heard of after  $4\frac{1}{4}$  years. Result: No improvement on discharge. ~~Ref. no. 122.~~ 'perfectly well, never needs a doctor'. Treatment: Arsenic.



36. M; age 18. Hospital 49 days. Symptoms first noticed 10 years before. Average case: Has had rheumatic fever and acute tonsilitis. Last heard of after 4 years. Result: Slight improvement on discharge. Now 'much better'. Treatment: Bromides, digitalis. Ref. no. 124.
37. F; age 33. Hospital 41 days. Symptoms first noticed 6 months before. Severe case: P. 120. Apical systolic murmur, insomnia. Last heard of after 2½ years. Result: Improved on discharge. Since leaving hospital has been in good health. No return of old complaint. Is married. Treatment: Belladonna, opium. Ref. no. 125.
38. F; age 13. Hospital 29 days. Symptoms first noticed 2 months before. Slight case, but had pneumonia and acute rheumatism. Admitted June 27, 1905; readmitted January 10, 1907, for palpitation. Other symptoms slight. Has had acute rheumatism several times. Last heard of after 15 years. Result: Is now attending out-patients. Her symptoms of exophthalmic goitre have improved. Treatment: Thymus tablets. Ref. no. 48.
39. F; age 19. Hospital 27 days. Average case. Last heard of after 3 years. Result: Better on discharge. Is now alive, but we cannot learn anything about state of health. Ref. no. 127.
40. F; age 27. Hospital 32 days. Symptoms first noticed 2 years before. Mild case as regards cardinal symptoms but had much headache, vomiting, and giddiness. Last heard of after 8½ years. Result: Better on discharge. Now writes: 'Am quite well, and have been ever since I left Guy's.' Went to service 4 years, and then married, 4 children. A credit to Guy's. Has never needed a doctor 'although she pays into a club'. Treatment: Belladonna, digitalis. Ref. no. 132.
41. F; age 32. Hospital 16 days. Symptoms first noticed 6 years before. Very mild case in all respects. Last heard of after 7½ years. Result: Better on discharge from Guy's. In 1905 went to King's College Hospital; was operated on and says she has been better since. Treatment: Rest and subsequent operation. Ref. no. 136.
42. F; age 29. Hospital 30 days. Symptoms first noticed 2 years before. Severe case: P. 140. Palpitation, pigmented skin, vomiting, and diarrhoea. Last heard of after 7 years. Result: Better on discharge. After that improved slowly. Now appears quite well. Treatment: Belladonna. Ref. no. 137.
43. F; age 39. Hospital 131 days. Symptoms first noticed 2½ years before. Severe case: P. 120. Wasting, pigmentation, vomiting, diarrhoea, sweating, systolic murmur. Last heard of after 6½ years. Result: Better on discharge. Is now better and stronger but has to be careful. Treatment: Belladonna, opium. Ref. no. 138.
44. F; age 53. Hospital 19 days. Symptoms first noticed 2 years before. Average case, but some diarrhoea and vomiting. Last heard of after 6 years. Result: Better on discharge and has continued to improve. Is sure rest does good. Treatment: Belladonna. Ref. no. 140.
45. F; age 19. Hospital 16 days. Symptoms first noticed 4 years before. Average case. Last heard of after 6 years. Result: Writes to say health has been fairly good and has felt better since operation. Treatment: The right lobe of thyroid was removed. Ref. no. 141.
46. F; age 18. Hospital 61 days. Symptoms first noticed 6 months before. Mild case. Last heard of after 5½ years. Result: Better on discharge. Now writes that she is much better as result of homoeopathic treatment. Treatment: Adrenalin, belladonna, digitalis. Ref. no. 142.
47. F; age 34. Hospital 73 days. Symptoms first noticed 1 year before. Severe case: Diarrhoea, vomiting. Last heard of after 5 years. Result: Better on discharge. Quite cured by an American goitre cure. Treatment: Moebius' serum, belladonna. Ref. no. 143.
48. F; age 25. Hospital 43 days. Symptoms first noticed 3 years before. Severe case: Sweating, wasting. Last heard of after 4½ years. Result: Better on discharge. Now all the symptoms have disappeared, except that there is slight enlargement of the thyroid. In 1906 married; has one child born same year. Attributes much of her improvement to her pregnancy. Treatment: Moebius' serum. Ref. no. 146.
49. F; age 34. Hospital 170 days. Symptoms first noticed 1½ years before. Wasting, otherwise mild case. Last heard of after 4 years. Result: Did not improve much in hospital but is now quite well, and began to improve when she began work four months after leaving hospital. Treatment: Moebius' serum. Ref. no. 149.
50. F; age 53. Hospital 21 days. Symptoms first noticed 10 years before. Average case: P. 138. Last heard of after 8 years. Result: Writes that she 'received great benefit from the operation' but 'my health is very bad at times'. Treatment: Operation—Isthmus and right lobe of thyroid removed. Ref. no. 162.
51. F. Hospital 9 days. Symptoms first noticed 2½ years before. Average case. Last heard of after 3½ years. Result: No improvement during 9 days' rest in hospital. Is now quite recovered, goitre has gone. Is married. Ref. no. 165.
52. F; age 23. Hospital 47 days. Symptoms first noticed 3 months before. Average case, but had diarrhoea. Last heard of after 3 years. Result: Better on discharge. Now

says 'perfectly well since operation'. Treatment: Operation—Right lobe of thyroid removed. *Ref. no. 168.*

53. F; age 23. Hospital 23 days. Symptoms first noticed 9 months before. Average case. Last heard of after 3 years. Result: Better on discharge. Now says still suffers from attacks of palpitation, but they are much less. Has greater self-control. Feels cold more than before operation. Since operation has been subject to attacks of dizziness and lassitude for the first twelve months almost daily, but they are getting less. Has been in doctor's hands since leaving hospital for a slight attack of anaemia. Treatment: Operation—Left lobe of thyroid removed. *Ref. no. 169.*
54. F; age 40. Hospital 44 days. Symptoms first noticed 11 years before. Mild case. Last heard of after 2½ years. Admitted for hysterectomy. Now writes: 'Much better.' Treatment: No special treatment for exophthalmic goitre. *Ref. no. 172.*

## TABLE B.

## FIFTY-SEVEN PRIVATE CASES.

The name in brackets is that of the doctor under whose care the patient was.

1. F; age 40. (Monier-Williams.) Average case: Slight thyroid enlargement and exophthalmos. Good weight. Much tachycardia, palpitation, and dyspnoea on exertion. Thick arteries, big heart, albumin and high tension (170). Last heard of after 5½ months. Result: Better. When in bed seems well. Eats, reads, and enjoys life. This is third long rest (many months) in bed. They did much good previously. Before first seemed to be dying. Treatment: Chiefly rest in bed. *Ref. no. 23-144.*
2. F; age 24. (H. A. Munro.) Bad case: Much thyroid, exophthalmos, tachycardia, and palpitation. Slight tremor. Very nervous and excited. Occasional albumin and oedema. Considerable Rigg's Disease. Last heard of after 5½ months. Result: A little better. But no inference should be drawn, for would not stay in bed and took serum irregularly. Treatment: Moebius' serum. *Ref. no. 23-170.*
3. F; age 19. (E. L. Adeney.) Bad case: Complicated with severe phthisis. Last heard of after 3 months. Result: Died from phthisis 3 months after being seen. *Ref. no. 23-210.*
4. F; age 35. (A. W. Soper.) Severe case: With all the chief symptoms. Very nervous and irritable. Last heard of after 7 months. Result: Exophthalmos and thyroid much better. Almost lost extreme nervousness and irritability. Normal in mental capacity. Heart sounds better. Tachycardia still present. Occasional dyspnoea, but still improving. Treatment: Bed 7 months, extra food, Moebius' serum. *Ref. no. 22-177.*
5. F; age 37. (C. C. Gibbes.) Moderate case: Slight thyroid, tachycardia. P. 120. Palpitation, slight cardiac dilatation, tremor. Very nervous. Fingers go pale and cold. No exophthalmos. Last heard of after 12 months. Result: Rest did a 'lot of good'. More peaceful and quiet. 'Now I get about more, but do not feel well yet.' Gained weight. Treatment: Bed 6 weeks. Moebius' serum did not appear to do good. *Ref. no. 21-258.*
6. F; age 30. (R. B. Duncan.) Very bad case: Big thyroid (neck round it 13½ in.), tachycardia. P. 140. Palpitation, much tremor, anaemia, and weakness. No improvement up to now on any treatment. No exophthalmos. Last heard of after 11 months. Result: Very much better able to attend to household and go out for short walks, but cannot hurry. P. 80-90. Neck 11½ in. Treatment: Bed 6 months. *Ref. no. 21-338.*
7. F; age 33. (A. E. Tonks.) Bad case: Huge thyroid, great exophthalmos, tachycardia, dilated heart, slight tremor. Last heard of after 19 months. Result: Much better. Expecting every day to go to bed to be confined. At end of 2 months P. 80 and exophthalmos less. Dr. Tonks thinks the rest, and not the serum, is responsible for improvement. Treatment: Bed many months, Moebius' serum. *Ref. no. 20-20.*
8. F; age not stated. (A. W. Soper.) Mild case: Considerable thyroid, moderate exophthalmos, tachycardia, and tremor. Last heard of after 18 months. Result: At end of 2 months quite cured. Thyroid, pulse, eyes normal. Still well at end of 18 months. Treatment: Bed for 2 months. *Ref. no. 20-331.*
9. F; age 44. (E. F. Hardenberg.) Average case: Thyroid normal, much exophthalmos and tachycardia. Weak tremor, dilated heart. Last heard of after 18 months. Result: Much better. At end of 6 months after rest able to work as schoolmistress fairly well. Much stronger. P. normal. Exophthalmos remains and has developed diplopia. Treatment: Prolonged rest. *Ref. no. 20-359.*
10. F; 35. (H. A. Burrowes.) Moderate case: Much exophthalmos, thyroid normal, tremors, tachycardia (P. 105). Very nervous. Last heard of after 18 months. Result: Soon began to improve. P. 80. Exophthalmos hardly noticeable. Irritability gone. For some time has been able to lead a normal quiet life. No tremor. Treatment: Rest every day, Moebius' serum. *Ref. no. 20-362.*
11. F; age 21. (Doctor's name missing.) Moderate case: Is slowly improving under rest. Has had some symptoms of it for 6 years. *Ref. no. 19-45.*

12. F. (Doctor's name missing.) Moderate case: Mother of No. 11; has got well with rest.  
*Ref. no. 19-45.*
13. F; age 49. (F. A. Brooks.) Moderate case: Tachycardia, slight thyroid, attacks of diarrhoea. Last heard of after 24 months. Result: No improvement, refuses rest and treatment.  
*Ref. no. 19-124.*
14. F; age 48. (F. Stephenson.) Moderate case: Much tachycardia (P. 120), thyroid, and tremors. Very nervous. Last heard of after 24 months. Result: Five months after much better. P. 90. Takes food well. Nervousness gone. Not being attended now, is well. Treatment: Rest in bed.  
*Ref. no. 19-262.*
15. F; age 48. (F. Evered.) Mild case: All cardinal symptoms. Last heard of after 23 months. Result: Excellent general health, takes average amount of exercise, not debarred from any social functions. Has gained weight. No symptoms of the disease except slight exophthalmos, which is lessening. Treatment: Rest in bed. This more efficacious than any other treatment.  
*Ref. no. 19-357.*
16. M; age not stated. (J. R. Watt.) Severe case: Tachycardia (P. 120), loss of weight, exophthalmos, tremor, no thyroid enlargement, diarrhoea. Last heard of after 23 months. Result: After 5 weeks' rest in bed improved, exophthalmos less, P. fell to 96. Gave up rest, lost what he had gained, and is now as he was when first seen. Treatment: Rest in bed and Moebius' serum.  
*Ref. no. 19-376.*
17. F; age 40. (R. W. Rouw.) Very severe case: Extreme exophthalmos, tachycardia (P. 120), tremor, slight thyroid. Last heard of after 33 months. Result: Cured, except exophthalmos still evident, but much diminished. Can walk 3 miles a day. P. 80-90. Thyroid normal. Rest in bed many months. Moebius' serum. No. 18-24.
18. M; age 24. (T. F. Woodroffe.) Severe case: Large thyroid, tachycardia (P. 140), cardiac dilatation, tremors. Last heard of after 32 months. Result: Completely cured. Treatment: Rest in bed and digitalis, but no improvement. When rest continued and Moebius' serum given 'wonderful improvement, pulse falling at once'.  
*Ref. no. 18-146.*
19. M; age 40. (G. F. Hugill.) Had exophthalmic goitre for years, and diabetes for last 12 months. Result: In spite of his diabetes the exophthalmic goitre has been getting better, and now no signs of it, except eyes a little prominent. Died of diabetetic coma a few days after I saw him.  
*Ref. no. 18-418.*
20. F; age 35. (G. Whiteley.) Moderate case: Marked exophthalmos and thyroid, tachycardia (P. 120), many miscarriages, dysmenorrhoea, wasted. Last heard of after 3½ years. Result: At end of 7 months had gained 28 lbs. P. 84 in morning. Much better. At end of 3 years said she was very much better. Treatment: Rest in bed 9 months.  
*Ref. no. 17-76.*
21. F; age 35. (M. J. Bulger.) Very severe case: Seven years ago left lobe of thyroid removed for exophthalmic goitre. Says she was better for a time, but soon got bad again. Now marked exophthalmos, tachycardia (P. 170). The remaining lobe has hypertrophied greatly. Too weak to stand; very thin, impulse outside nipple. Last heard of after 3½ years. Result: Slowly got better, and when heard of 3½ years after was able to walk to business and do a hard day's work. She has a sister (whom I saw) who had the disease at the same time as patient was operated upon. This sister slowly got well, and has remained so till now (1910). A brother also has the disease. Treatment: Rest in bed 4 months after I saw her; also took arsenic.  
*Ref. no. 17-77.*
22. F; age 26. (R. Tilbury.) Severe case: Marked exophthalmos, thyroid, and tachycardia. Last heard of after 1½ years. Result: Very much better in all respects, and got well enough to go with her husband to South Africa. Treatment: Rest in bed 4 months.  
*Ref. no. 17-389.*
23. F; age 39. (J. P. Pendlebury.) Average case: Much loss of weight and insomnia. Exophthalmos, thyroid, tachycardia moderate. Last heard of after 3½ years. Result: Much better. Enjoys very fair health. Occasional palpitation, but only after over-exertion. Attends many social functions. Signs of exophthalmic goitre slight. Well nourished. Treatment: Rest in bed for some weeks.  
*Ref. no. 16-67.*
24. F; age 15. (Stanley Smith.) Average case: Considerable exophthalmos, tachycardia, and thyroid; very nervous and excitable. Some cardiac dilatation. Last heard of after 3½ years. Result: Very well, able to take her ordinary part in life. Going to be married. Pulse and thyroid normal. Eyes slight exophthalmos. Treatment: Rest in bed many months.  
*Ref. no. 16-157.*
25. F; age 34. (Fraser Nash.) Mild case: All the usual symptoms. P. 130. Last heard of after 3½ years. Result: Improved in every way, but still feels nervous when out alone. After a few weeks' rest improvement very evident. P. 96. Thyroid normal, slight exophthalmos. Treatment: Rest in bed a few weeks.  
*Ref. no. 16-304.*
26. F; age 30. (E. F. Heap.) Severe case: Extreme nervous symptoms, great tremor, much weeping, considerable thyroid. P. 90. Last heard of after 4½ years. Result: Well, leading active life, but easily excited and then slight tremor visible. Gradually got quite well, and has been so for 2 years. Treatment: Rest in bed a few weeks, then very quiet life with much rest on the Riviera.  
*Ref. no. 15-145.*
27. F; age 63. (G. Levick.) Very severe case: Slight exophthalmos, some tremor, extreme

- tachycardia (150-160), trace albumin, general oedema, wasting, fluid in pleura. Result: Died 14 days after I saw her, suddenly. The pleural effusion increased rapidly, but aspiration was not allowed. *Ref. no. 15-279.*
28. F; age 45. (R. G. Hicks.) Slight case in all respects. Result: Left England after rest, but Dr. H. has heard that she is highly nervous and easily excited, but otherwise well. Treatment: Rest. *Ref. no. 14-128.*
29. F; age 17. (R. Kirkland and F. Hinds.) Average case: Large thyroid, slight exophthalmos, some tachycardia (P. 130), slight tremor. Last heard of after  $5\frac{1}{2}$  years. Result: Very good health, thyroid and eyes normal, good weight, able to go to dances. Treatment: Rest in bed some months, belladonna. *Ref. no. 13-132.*
30. F; age 22. (F. Hinds.) Average case: Large thyroid, no exophthalmos; tremor, anaemia, wasting, all present; extreme tachycardia. Last heard of after  $5\frac{1}{2}$  years. Result: Very good health, thyroid and eyes normal, good weight, busy from 7 a.m. to 10 p.m. Treatment: Rest in bed some months. *Ref. no. 13-260.*
31. F. (Doctor's name missing.) Severe case: Large thyroid, slight exophthalmos and tremor, some tachycardia, some diarrhoea. Last heard of after 1 year. Result: 'Did very well.' Cannot be traced after 1 year. Treatment: Rest. *Ref. no. 12-158.*
32. F; age 33. (Newlyn Smith.) Average case: Slight thyroid and exophthalmos, much tachycardia and tremor. Last heard of after  $5\frac{3}{4}$  years. Result: Certainly improved upon rest, but there is every probability that this was not carried out for long. When last seen, 1907, she was much the same as in 1905. Now (1910) writes: 'Getting on fairly well, leading quiet country life.' Treatment: Rest for a time; also arsenic, bromide, and iron. *Ref. no. 12-208.*
33. F; age 40. (C. J. Woollett.) Moderate case: Patient drinks. Last heard of after 1 year. Result: Died from alcoholism a year after I saw her. *Ref. no. 11-101.*
34. F; age 29. (T. B. Scott.) Very severe case: Exophthalmic goitre for some time. Latterly thyroid and exophthalmos much less, but loud mitral murmur has appeared. She now has great oedema of feet, relieved by Southey's tubes. Very nervous. Last heard of after 1 year. Result: Dr. Scott wrote: 'She got practically well gradually, and is now at home in New Zealand.' Treatment: Rest, digitalis. *Ref. no. 11-200.*
35. F; age 39. (J. F. Hossack.) Mild case in all respects. Result: Passed out of Dr. H.'s hands, but he sees her in the street, and she appears well. Treatment: No note. *Ref. no. 11-208.*
36. M; age 46. (S. Wachter.) Average case: Exophthalmos, tremor, tachycardia, slight wasting, diarrhoea. Last heard of after  $6\frac{1}{2}$  years. Result: Recovered to all intents and purposes. Can go for long walks. Recovery gradual. Treatment: Rest, and then a sea trip. *Ref. no. 11-349.*
37. F; age 27. (H. F. Vincent and J. S. Richards.) Mild case in all respects. Last heard of after  $6\frac{1}{2}$  years. Result: Recovered completely from exophthalmic goitre. But has degenerated into complete invalid; an introspective, selfish neurasthenic. Treatment: Occasional rest, but no treatment was continued for long. *Ref. no. 11-366.*
38. F; age 30. (R. Alexander.) Mild case of exophthalmic goitre in all respects. She did not come for this but for headaches. Last heard of after  $7\frac{1}{2}$  years. Result: Exophthalmic goitre no more pronounced. Treatment: None special. *Ref. no. 10-52.*
39. F; age 23. (A. Matcham.) Very severe case: Lost 3 st. last 18 months. Much thyroid and exophthalmos and tachycardia (P. 130), T. 99-2°, tremor, frequent severe diarrhoea. Last heard of after  $7\frac{1}{2}$  years. Result: Got quite well, put on flesh, and remains well to present time. Dr. M. attributes her recovery to the thyroid. Treatment: Poor woman, who could not rest. Thyroid gr. v 3 times a day for 3 months, then gr. x 3 times a day for a year. Went into country. *Ref. no. 10-72.*
40. F; age 19. (E. R. Fothergill.) Mild case: Enlarged thyroid, no exophthalmos, tremor, tachycardia. Last heard of after 7 years. Result: Got quite well as result of rest, and has remained well. Now (1910) looks quite well in all respects. Is married, and expecting her confinement. Treatment: Rest in bed 6 weeks. *Ref. no. 10-235.*
41. M; age 30. (P. J. Lush.) Very severe case: Acute exophthalmic goitre following influenza. Thyroid has enlarged much in 14 days. P. 100, impulse nipple line, T. 99°, slight exophthalmos, great tremor, exceedingly restless, so bad it was thought he would die. Last heard of after  $6\frac{3}{4}$  years. Result: Got quite well. Within 12 months was riding across country, and has remained well ever since. Treatment: Restlessness controlled by hyoscine and was kept in bed many months. *Ref. no. 10-378.*
42. F; age 18. (S. C. Austin.) Moderate case: Tachycardia, tremor, enlarged thyroid, very slight exophthalmos. Last heard of after  $5\frac{1}{2}$  years. Result: Got quite well, and has remained well since. Is now married. Treatment: Poor girl; could not rest. No special treatment. *Ref. no. 10-393.*
43. F; age 35. (H. M. Stewart and G. B. Batten.) Moderate case: Tachycardia (P. 150-160), tremor, moderate thyroid, slight exophthalmos. Last heard of after  $8\frac{1}{2}$  years. Result: Much better than she was. Is able to do her work, but not well. Treatment: Could not rest. No special treatment, except that lately she has had 75 applications of X-rays over thyroid. This improved her. *Ref. no. 9-32.*

44. F; age 27. (R. H. W. Wilbe.) Severe case: Followed influenza, much wasting, tachycardia (P. 110), impulse outside nipple, large thyroid, moderate exophthalmos, insomnia. Last heard of after 3 years. Result: Got quite well. Treatment: Rest in bed, feeding. Faradism to neck (this did no good). Later on massage. *Ref. no. 9-155.*
45. F; age 31. (W. W. Wingate.) Severe case: Big thyroid, great tremor, tachycardia, some exophthalmos. Last heard of after 8 years. Result: For some months very quiet life. Greatly improved, eyes and thyroid became almost normal. In 1908 was discovered to have diabetes, from which she died in 2 months. Treatment: Rest. *Ref. no. 9-265.*
46. F; age 25. (W. A. Brailey.) Severe case: Much tremor, exophthalmos, thyroid, and tachycardia. Heart much dilated. Has had rheumatic fever. Sister of 4-57, who died. Result: Improved very much, but while the improvement was progressing I lost touch of the case. Treatment: Rest in bed. Cannot be traced for long. *Ref. no. 9-293.*
47. F; age 27. (E. L. Adeney.) Average case: Much tremor, some diarrhoea. Result: 'Improved for a time with rest, and died subsequently from diarrhoea.' Treatment: Rest. *Ref. no. 8-39.*
48. F; age 57. (E. R. Carter.) Many years ago was under Sir S. Wilks for exophthalmic goitre. She also had a fibroid of uterus. The thyroid and fibroid shrank together. Now the only evidence of the disease is some but not much exophthalmos. She is thin and liable to diarrhoea. Result: I saw her for lobar pneumonia. Severe case. She completely recovered, and the pneumonia did not lead to any return of the exophthalmic goitre. *Ref. no. 8-167.*
49. F; age 34. (F. H. Hollingshead.) Very severe case: Much thyroid and tachycardia, impulse nipple line, systolic murmur, slight exophthalmos, great tremor, very thin, much diarrhoea. Last heard of after 11½ years. Result: Gained 13 lb. in 2 months, and in that time got much better. Seen July 16, 1899. Much better. Dr. H. writes March, 1910: 'Much better I believe, but I have not seen her for several years.' Treatment: Rest in bed 2 months. *Ref. no. 6-190.*
50. F; age 21. (C. A. Ensor.) Severe case: Exophthalmos, thyroid, tremor, tachycardia, all present. Diarrhoea, urticaria. Six months later glycosuria appeared. Irritable. Last heard of after 14 years. Result: 6 months later better. Glycosuria persisted 2 years, but was not found after this time. By 1898 was 'practically well', could walk 8 miles. Slight tachycardia, thyroid, exophthalmos and irritability, but by 1899 normal in all these respects. 1910, normal in every way. P. 72. Thyroid normal, no tremor, no glycosuria. Eyes somewhat prominent. General health excellent. Treatment: Rest. *Ref. no. 5-35.*
51. M; age 32. (W. Howells.) Severe case: Much thyroid, exophthalmos, tachycardia, and tremor. Very nervous. Disease attributed to influenza. Much cardiac dilatation and wasting. Polyuria, no sugar or albumin. Last heard of after 5 years. Result: Got much oedema, because the cardiac symptoms became very severe, and it was thought he would die, but by the end of three years was quite well and back at business. Treatment: Prolonged complete rest. *Ref. no. 5-301.*
52. F; age 15. (W. A. Brailey.) Severe case: Much thyroid, exophthalmos, tachycardia, and very nervous. Took food badly. In spite of all treatment the cardiac dilatation became extreme and the most troublesome feature. Last heard of after 6½ years. Result: Died, October 23, 1900. The dilatation of the heart and the resulting symptoms were very severe, and probably the cause of death. Treatment: Prolonged rest, various drugs. *Ref. no. 4-57.*
53. F; age 32. (Kinsey-Taylor.) Average case: Very nervous. All usual symptoms present. Last heard of after 16 years. Result: Seen 6 months after operation. Feels better. Exophthalmos less, but tachycardia well marked. Cardiac dilatation unaltered, likewise nervousness. The left lobe of thyroid has grown bigger since operation. Sixteen years after operation 'distinctly better. No exophthalmos. Some tachycardia and palpitation. Nervous symptoms much the same. Still odd mentally'. Treatment: Right lobe of thyroid removed. *Ref. no. 4-97.*
54. F; age 20. (L. Roper.) Very severe case: Disease has lasted 5 years. Much exophthalmos, diarrhoea, tremor. Very large thyroid, neck 17 inches. Much cardiac dilatation. Gets syncopal attacks. The thyroid presses on trachea and renders breathing very difficult. Cannot lie down. The isthmus was merely a fibrous band. Last heard of after 5 years. Result: Dyspnoea much relieved by operation. Could lie down, heart less rapid. Saw her 18 months later and then, although still a severe case, she was undoubtedly better. Heard from Dr. A. Caddy (Calcutta) in 1899 that he had just seen her, who reported: 'Is in fairly good health, her symptoms have much lessened.' Treatment: Isthmus divided. Local anaesthetic as general considered too dangerous. Rested as much as possible, but this was not as complete as could be wished. *Ref. no. 4-185.*
55. F; age 27. (W. Wcaver.) Very severe case: Much exophthalmos, insertion of recti visible, large thyroid, much tremor, tachycardia (P. 150). Impulse outside nipple, loud systolic murmur. Much wasting. Result: 'Did well.' Treatment: Rest in bed, thyroid. *Ref. no. 4-305.*
56. F; age 29. (C. F. Routh.) Average case: Enlarged thyroid, moderate exophthalmos,

tachycardia (P. 130), cardiac dilatation, impulse outside nipple. Last heard of after 15 years. Result: Got quite well. Is still well in 1910. Treatment: 3 months' rest in bed, thymus. *Ref. no. 4-355.*

57. A severe case: I was present at the operation of removing the right lobe of the thyroid. Just after this had been done, but before the wound was closed, the patient, while still under the anaesthetic, died.

## TABLE C.

## TWENTY-ONE CASES THAT DIED IN THE HOSPITAL.

1. F; age 31. Hospital 14 days. Symptoms, ordinary: Been ill 18 months. Exophthalmos, tachycardia, palpitation, thyroid, all considerable. Special: Much palpitation, diarrhoea, vomiting. Course: Palpitation, diarrhoea, and vomiting, all got worse. Terminal pyrexia and jaundice. P. M. appearances: Gastro-enteritis, broncho-pneumonia. Treatment: Rest in bed, bismuth, strophanthus. *Ref. no. 1.*
2. F; age 24. Hospital 60 days. Symptoms, ordinary: Been ill 15 months, ordinary symptoms average. Special: great weakness. Course: Diarrhoea and vomiting set in and progressed. Slight jaundice. P. M. appearances: Large thymus, gastro-enteritis. Treatment: Rest in bed, galvanism to neck, bromides, belladonna. *Ref. no. 5.*
3. F; age 23. Hospital 2 days. Symptoms, ordinary: Ill 6 months, ordinary symptoms considerable. Special: Very rapid pulse, much weakness and vomiting. Course: Vomiting persisted. P. M. appearances: Large thymus. *Ref. no. 9.*
4. F; age 54. Hospital 13 days. Symptoms, ordinary: Ill 6 months, ordinary symptoms average. Special: Much palpitation, mitral regurgitation. Course: The cardiac trouble became worse and was the cause of death. P. M. appearances: Large left ventricle. Treatment: Rest in bed, digitalis. *Ref. no. 10.*
5. F; age 30. Hospital 9 days. Symptoms, ordinary: Ill 12 months, ordinary symptoms considerable. Special: Patient anxious for operation because exophthalmos prevented her following her occupation as barmaid. Course: A. C. E. given, right lobe removed. Next day extremely excitable. T. 103°. Death. P. M. appearances: Nothing to explain death. Treatment: Operation. *Ref. no. 38.*
6. F; age 22. Hospital 4 days. Symptoms, ordinary: Symptoms of exophthalmic goitre for 7 years. Special: Came in for rheumatic fever. P. 150. Course: Got rapidly worse and died apparently from severe rheumatic fever. P. M. appearances: Thymus persistent, Peyer's patches prominent. Treatment: For rheumatic fever. *Ref. no. 52.*
7. F; age 32. Hospital 59 days. Symptoms, ordinary: Average case. Special: Much headache. Course: Headache became very severe, also much vomiting. P. M. appearances: Thrombosis right middle cerebral artery and consequent softening. Treatment: Rest in bed, belladonna, opium. *Ref. no. 23 a.*
8. F; age 36. Hospital 19 days. Symptoms, ordinary: Severe case. Special: Apical systolic murmur, diarrhoea. Course: Diarrhoea. Delirious for 14 days before death. P. M. appearances: No cause for death found. Treatment: Rest in bed, belladonna, digitalis. *Ref. no. 53.*
9. F; age 37. Hospital 7 days. Symptoms, ordinary: Been ill 9 months. Pulse 130-150. Other ordinary symptoms average. Special: Great weakness, apical systolic murmur. Attributes onset of exophthalmic goitre to an attack of rheumatic fever. Course: Became delirious and cyanotic. Died suddenly. P. M. appearances: Thymus large, no endocarditis. Treatment: Rest in bed, Leiter's coils, belladonna. *Ref. no. 62.*
10. F; age 26. Hospital 15 days. Symptoms, ordinary: Ill 2 months. Average case. Special: Admitted for rheumatic fever and pericarditis. Course: Diarrhoea supervened. Became delirious. P. M. appearances: Endocarditis, pericarditis. *Ref. no. 71.*
11. F; age 24. Hospital 39 days. Symptoms, ordinary: Ill 11 months. Average case. Special: Had pneumonia with delirium. Course: Vomiting and diarrhoea supervened. P. M. appearances: No post mortem. *Ref. no. 80.*
12. F; age 26. Hospital 27 days. Symptoms, ordinary: Ill 20 months. Severe case. Special: Much dyspnoea, became melancholic. Course: Diarrhoea, delirium, and pyrexia supervened. P. M. appearances: Trachea compressed by thyroid. Treatment: Rest in bed, belladonna, digitalis, bromides. *Ref. no. 81.*
13. F; age 41. Hospital 13 days. Symptoms, ordinary: Ill 8 years, ordinary symptoms slight. Special: Diabetes discovered soon after onset of exophthalmic goitre. Course: Had had both diseases 8 years, died of coma. P. M. appearances: Old endocarditis. *Ref. no. 83.*
14. F; age 25. Hospital 24 days. Symptoms, ordinary: Ill 18 months, ordinary symptoms moderate. Special: Weakness, had mania and later pneumonia. Course: Died from pneumonia. P. M. appearances: Lobar pneumonia. *Ref. no. 86.*

15. F; age 33. Hospital 83 days. Symptoms, ordinary: Ill 2 years, ordinary symptoms average. Special: Much wasting, delirium, vomiting, and diarrhoea. Course: Died from cardiac weakness. P. M. appearances: Broncho-pneumonia. Treatment: Rest in bed, belladonna, digitalis. *Ref. no. 103.*
16. F; age 22. Hospital 47 days. Symptoms, ordinary: Ill 9 months, ordinary symptoms moderate. Special: Melancholia, vomiting, and diarrhoea. Course: The vomiting and diarrhoea increased and delirium supervened. P. M. appearances: Thymus enlarged. Treatment: Rest in bed, belladonna, digitalis, opium. *Ref. no. 110.*
17. F; age 27. Hospital 18 days. Symptoms, ordinary: Average. Special: None. Course: Became comatose and died. P. M. appearances: Report missing. No. 111.
18. F; age 27. Hospital 5 days. Symptoms, ordinary: Very severe. Special: Vomiting, very severe tremor. P. 192. P. M. appearances: Nothing found to explain death. *Ref. no. 118.*
19. F; age 21. Hospital 59 days. Symptoms, ordinary: Average, but much tremor. Special: Vomiting, jaundice. T. 102. P. M. appearances: Liver small, bile stained, acute ascending nephritis due to *Bacillus coli*. Treatment: Belladonna, strophanthus. *Ref. no. 150.*
20. F; age 19. Hospital 9 days. Symptoms, ordinary: Average. Special: Diarrhoea. Course: Cocaine used locally, chloroform given, right lobe and isthmus excised. Died day after operation. No post mortem. Treatment: Operation. *Ref. no. 166.*
21. F; age 29. Hospital 30 days. Symptoms, ordinary: Average. Special: Much sweating, also diarrhoea. Course: Eucaïne and adrenalin locally and chloroform, both superior thyroids tied. Later, under same anaesthetic, attempt to tie inferior thyroids. Patient died on the table. P. M. appearances: Enlarged thymus, fatty infiltration of heart. Treatment: Operation. *Ref. no. 167.*

# ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

## MINUTES OF PROCEEDINGS OF ANNUAL GENERAL MEETING, 1910, HELD AT LIVERPOOL.

THE FOURTH ANNUAL GENERAL MEETING was held at Liverpool on Thursday and Friday, June 2 and 3, 1910, in the Medical Institution. At 10 a.m. the President, Professor Little, took the chair. The minutes of the last meeting were confirmed. The President and Officers of the Association were elected by ballot as follows:—

President: Professor Glynn.

Treasurer: Dr. Hale White.

Secretary: Dr. Herringham.

Members of the Committee:—

For England: Dr. Judson Bury.

Dr. William Collier.

Dr. Garrod.

Dr. Wardrop Griffith.

Dr. Hutchison.

For Scotland: Dr. Alexander Bruce.

Professor Finlay.

Dr. W. K. Hunter.

For Ireland: Sir John Moore.

Dr. William Calwell.

Dr. J. F. O'Carroll.

The President, Professor Glynn, then took the chair.

The following new members were elected by ballot:—Dr. A. W. Falconer, Dr. W. MacLennan, Dr. John Owen, Dr. Lloyd Roberts, Dr. F. Meadows Turner.

Dr. Richard Caton was elected an honorary member.

The Treasurer then presented his accounts, which were received and adopted.

It was resolved—That a sum not exceeding £50 be allowed to the Editors of the QUARTERLY JOURNAL OF MEDICINE for the purpose of obtaining Reviews of special subjects, to be published in the said Journal.

That the next Annual General Meeting be held in London.

It was announced by the President that a suggestion had been made for a joint meeting with the Association of American Physicians next year. It was resolved that this be referred to the Executive Committee with power to act.

It was further resolved—That notice of any proposal to amend or alter the existing rules, or to pass new rules, must be sent to the Secretary not later than one month before the next ensuing General Meeting, and must appear on the agenda of the said meeting in the form of a motion.



That non-attendance at the present meeting, which, owing to the death of the late King, had been postponed from May 19 and 20, should not count as non-attendance under Rule 20, but that attendance at this meeting, or a notification of intention to be present at the original date, should count as an attendance.

The scientific business then began, and the following communications were made:—

*Metabolism during the use of Nutrient and of simple Saline Enemata* (Dr. Langdon Brown), showing that Metabolism, as measured by N output and the production of Diacetic acid, is not materially different under Nutrient and Saline Enemata respectively. This was discussed by Dr. Stacey Wilson.

*Pathological variations of the Secretory Activity of the Stomach* (Dr. Craven Moore and Dr. Kilroe). Professor Saundby spoke.

*Gastrostaxis and Menstruation* (Dr. Sutherland). The speaker suggested (1) that bleeding during Menstruation may cause one form of hæmatemesis; (2) that this occurs apart from ulceration, and is due to vaso-motor disturbance; (3) that the use of saline aperients before the menstrual period may serve as a preventive of such bleeding. The communication gave rise to a lively discussion in which the following took part:—Professor Saundby, Drs. Hertz, Cowan, Stacey Wilson, Craven Moore, Gullan, Hale White, and Byrom Bramwell.

*The Cardinal Factor in Infant Feeding* (Dr. David Forsyth). The speaker laid stress upon the importance of the surface area in estimating the nutritive requirements of infancy. Dr. Robert Hutchison criticized some of the statements made. Dr. Stacey Wilson also spoke.

The meeting then adjourned to the Lantern Room for the following communications:—

*Disorders of the Motor Functions of the Stomach* (Dr. A. Hertz) from the results of X-ray Examinations.

*A case of Chronic Interstitial Pneumonia* (Dr. Arthur Hall and Professor Beattie).

From 12.45 to 1.20 p.m. Demonstrations were given at the Royal Infirmary.

1. *X-rays*—Mr. Thurston Holland.

2. *Rare Throat Cases*—Dr. Middlemass Hunt.

3. *Ophthalmic Cases and Apparatus for testing Colour Blindness*—Dr. Karl Grossmann.

4. *Segregation of Urine*—Mr. R. A. Bickersteth.

The Afternoon Session was held at 3 p.m., when the following communications were made:—

*Acute Ascending Paralysis after Influenza* (Dr. E. S. Reynolds). A description of four cases with recovery. Dr. Farquhar Buzzard discussed the diagnosis. Drs. Donovan and Hawthorne and Professor Michell Clarke also spoke.

*Some Cases of Tuberculous Meningitis in Adults* (Dr. Warrington). The peculiarities of Tuberculous Meningitis in adults were discussed by Drs. Lawson, Parkes Weber, Professor Saundby, Drs. Nathan Raw, Purves Stewart, Sir Thomas Barlow, Frederick Taylor, Hale White, and Byrom Bramwell.

*Cerebro-spinal Meningitis treated with Meningococci Vaccine* (Dr. Bradshaw), recording a successful case. Drs. Warrington, Ramsbottom, Frederick Taylor, Professors George Murray and Saundby, and Dr. Claude Ker discussed the treatment.

*The effect of Mercurial Injections in the treatment of Locomotor Ataxia* (Dr. Gordon Gullan), in which the method was recommended in early cases with illustrative

instances. Drs. Farquhar Buzzard and Warrington recommended the method, while Dr. Theodore Thompson reported negative results from its use.

After an interval for tea the Meeting was resumed in the Lantern Room, when the following demonstrations were given :—

*Tuberosc Sclerosis* (Dr. J. S. Fowler), a description of the pathological features of this rare disease. Sir Thomas Barlow spoke.

*Recurrent Motor Paralysis during attacks of Migraine* (Professor Michell Clarke), describing a family in which several members in different generations were affected. Dr. Purves Stewart described similar cases in individuals.

*Haemorrhagic Encephalitis* (Dr. Byrom Bramwell), a case with post-mortem examination. Dr. Reynolds and Professor Little spoke.

The Meeting then adjourned.

The Annual Dinner was held at 7.15 p.m. in the Adelphi Hotel. The toast of The Association was proposed by Archdeacon Madden and responded to by Sir Thomas Barlow. The other toasts were The Guests, The President, and The Hon. Secretaries.

The Meeting resumed on Friday at 10 a.m. Sir Samuel Wilks was elected an honorary member of the Association.

The following communications were made :—

*Two cases of Glandular Enlargement of unusual type* (Dr. W. K. Hunter), with sections of the glands. Dr. William Hunter spoke.

*Erythema and Lesions of Joints* (Dr. Garrod). It was suggested that this combination was toxic rather than infective. Drs. Campbell McClure, Symes, Leonard Guthrie, and Professor Stockman spoke.

*The Acidity of the Urine in Phthisis* (Drs. Lawson and Lea). Professor Saundby, Drs. Stacey Wilson, Gossage, and Hale White spoke.

*The Granular and the Sclerotic Kidney*. Sir Clifford Allbutt gave a general exposition of his views on the relationship of these forms of renal disease. Professor Lorrain Smith demonstrated macro- and microscopic preparations. A prolonged discussion followed, in which the following took part :—Drs. Cowan, Theodore Thompson, Stacey Wilson, Professor Saundby, Drs. Hawthorne and Samuel West.

The Meeting then adjourned to the Lantern Room for demonstrations :—

*Induced Cell Proliferation and its relation to Normal Healing and to Malignancy* (Drs. Macalister and H. C. Ross). .

*A method of estimating Calcium in the Blood* (Drs. Blair Bell and Pantland Hick).

*A Urine containing a hitherto undescribed Protein* (Dr. G. S. Middleton).

The Meeting then adjourned.

Friday afternoon was devoted to Diseases of the Heart, and the Meeting took place for the most part in the Lantern Room. The following communications were given :—

*The meaning of the audible signs in Mitral Stenosis* (Dr. Alexander Morison). Drs. Stacey Wilson, John Hay, and Bradshaw spoke.

*A case of Sarcoma of the Heart* (Dr. Nathan Raw). Drs. Morrison and Travers Smith spoke.

*The Factors which determine the Size of the Heart* (Professor Dreyer and Dr. W. Ray).

*The Hypertrophy of the Heart due to work* (Professor Dreyer and Dr. A. G. Gibson). Dr. Tyson spoke.

*Two cases of Acute Endocarditis in which the a-v bundle was involved* (Drs. Cowan, Teacher, and Kennedy). Professor Allbutt, Drs. Gossage, Hay, Coombs, and Professor Griffith spoke.

*Coupled Rhythms* (Drs. Cowan and W. T. Ritchie). Dr. Stacey Wilson spoke.

*Adams-Stokes Disease; a short series of cases* (Dr. Hay). The cases were discussed by Drs. Gossage and Hay and the President.

*The production of complete Heart-block by the administration of large doses of Strophanthus* (Dr. Emanuel). Drs. Stacey Wilson and Hay spoke.

*The Pulse immediately preceding the Epileptic Attack* (Dr. A. G. Gibson).

It being past six o'clock, the Association adjourned after a vote of thanks to the President and Secretaries.

# THE BACTERIOLOGY OF HUMAN BILE WITH ESPECIAL REFERENCE TO THE TYPHOID CARRIER PROBLEM

By J. F. WINDSOR

(From the Pathological Laboratory, St. Thomas's Hospital)

## *Summary of previous work.*

It was formerly supposed that bile possessed a mild antiseptic action and that therefore bacteria would not thrive in it, and frequently it has been stated that the bile of man and of animals is normally sterile; in the case of animals experiments seem to bear out this statement, but there are obvious difficulties in the way of examining the bile of normal healthy persons during life, and therefore it cannot with any certainty be claimed that the bile of man is sterile; the study of bacteriology has, however, shown that bile possesses very little antiseptic property, and that for certain organisms, such as *Bacillus typhosus* and *Bacillus coli*, it forms a fairly suitable medium, though the rate of growth is not so rapid as in broth. The bile of patients suffering from inflammation of the gall-bladder has often been examined during life, and almost always has been found to be infected; Naunyn (16), Gilbert and Girode (9), and Martha (14) all found *Bacillus coli*, Terrier (19) found *Bacillus coli* and *Streptococcus pyogenes*, whilst Netter (14) found *staphylococcus* and *streptococcus*. Mieczkowski, quoted by Moynihan (15), examined the bile from 15 cases at the time of operation for diseases other than cholelithiasis and found it sterile in all, and of 23 cases operated on for cholelithiasis he found it infected in 18. Examinations of bile removed from the gall-bladder after death have been attended with varying results: Naunyn (16) found it to be sterile in both his cases, and Gilbert and Girode (9) found it sterile in six cases out of eight, but Ehret and Stolz (7) obtained very different results, for, using large quantities of bile, they found it sterile in only about one-half their cases. Fraenkel and Krause are said by Herter (10) to have found it sterile in 105 cases of 125 examined: of these 105 patients 36 were tuberculous and their bile was sterile when examined by the ordinary culture methods, but after injection into 11 guinea-pigs tuberculous lesions developed in 5, from which it seems that organisms may be present though not revealed by the ordinary culture methods.

These results point to the conclusion that bile examined after death is infected more often than not, especially when there is disease of the gall-bladder or its ducts, and it must be borne in mind that there is great difficulty in discovering certain organisms, such as the *pneumococcus* and *Bacillus*

tuberculosis, which makes it possible that the bile may appear to be sterile when in reality it is infected. Herter (10) says that bacteria are likely to be present in human bile even when there exist pathological conditions in parts remote from the gall-bladder, and that perhaps their presence may frequently be regarded as evidence of terminal infection rather than as the expression of an earlier invasion. Stagnation of bile increases the chance that bacteria will establish themselves in the vicinity of the gall-bladder, and this has been asserted to be one of the causes of the more common occurrence of gall-stones in women than in men, obstruction to the expulsion of bile being attributed to tight-lacing. Charcot and Gombault (2), Naunyn (16), and Sherrington (18), experimenting on animals, showed that the bile remains sterile only so long as it flows unhindered through its ducts; after ligature of the common duct the bile speedily becomes infected.

According to Moynihan (15), it was Bernheim who first drew attention to the connexion between typhoid fever and biliary infection: clinical evidence shows that, after the fever has subsided, biliary colic is a not uncommon sequel, and a large number of patients suffering from cholelithiasis give a history of typhoid fever. Cushing (3) reported that 30 per cent. of the patients operated on at the Johns Hopkins hospital for cholelithiasis had at some time passed through an attack of enteric fever, and 20 per cent. of Chauffard's cases gave the same history. Furthermore at autopsies cholecystitis has been found in subjects with a previous history of typhoid fever, and from the contents of the gall-bladders of some have been isolated typhoid bacilli, which may reasonably be assumed to be the direct descendants of the original infective agents; Ehret and Stolz (7) collected thirty-two cases of typhoidal cholecystitis which were treated by operation or recognized post-mortem, in twenty of which gall-stones were present. This frequent association of cholecystitis with previous typhoid fever has led during recent years to a more regular and systematic bacteriological examination of the contents of the gall-bladder at the time of operation for cholelithiasis, with the result that *Bacillus typhosus* has frequently been found. Moynihan (15) operated on seven patients for gall-stones, all of whom gave a history of typhoid fever, and in the bile of two *B. typhosus* was found; he also quotes the investigations of Hartmann, who examined the bile in 46 cases and found it infected in 36, *B. coli* being present alone in 23 and associated with *Staphylococcus pyogenes aureus* in 2, whilst from the remainder were isolated either streptococcus or staphylococcus, *B. typhosus* not being once found. Petersen, quoted in the same paper, also failed to find *B. typhosus*, although the bile was infected in 44 cases out of 50, *B. coli* being present in all 44—in 36 alone, and in the remaining 8 associated with streptococcus or staphylococcus. Cushing (3), on the other hand, reported 7 cases of cholelithiasis all with a history of typhoid fever, in 2 of which *B. typhosus* was isolated, *B. coli* being isolated from the other 5; and Dudgeon (6) examined the bile from 20 cases operated on for cholelithiasis, finding *B. typhosus* once, *B. paratyphosus* B once, and in a third case a bacillus which was indistin-

guishable from *B. typhosus* culturally, but which gave negative agglutination reactions.

An important point is the very long period during which the organism of typhoid fever can apparently survive in the gall-bladder, for Hunner (12) isolated it in pure culture from a purulent collection in the gall-bladder of a patient eighteen years after an attack of typhoid, and Droba too is stated by Moynihan (15) to have found it seventeen years after the illness. Additional interest attaches to this extraordinary power of endurance of *Bacillus typhosus* in the gall-bladder owing to the discovery during the last few years of 'chronic typhoid carriers', to whom have been traced many sporadic cases and outbreaks of enteric fever, the origin of which used to be so great a mystery: it is sufficient here to mention the work of A. and J. C. G. Ledingham (13), who traced 31 cases occurring during four years in an asylum to three inmates, of whom two had had typhoid fever, whilst Davies and Hall (4) traced two outbreaks occurring in two different institutions to a carrier, who had served in both places either as cook or dairymaid, and Dean (5) reported the case of a patient in whose faeces he found *Bacillus typhosus* twenty-nine years after an attack of the fever. The problem arises as to where and how the organism manages to exist in the bodies of such carriers during so many years; it is not always to be found in the excreta, but only at intervals, and it is clear that there must be some central focus in which, once established, it can thrive and maintain an existence, and from which by some means it obtains passage into the intestinal tract. The evidence seems to point to the gall-bladder as the site of this central focus.

It is a well-known fact that *Bacillus typhosus* can frequently be recovered from the gall-bladder of patients who have died during the acute stages of typhoid fever: Cushing found it in 50 per cent. of his cases, Chiari in 19 out of 22, according to Moynihan, and Forster and Kayser, quoted by Kutchser (8), in 7 out of 8 cases. Moreover, post-mortem research has shown that, when death has occurred during an advanced stage of convalescence, the same organism has been recovered from the gall-bladder though no longer demonstrable in the spleen, and as shown by Hunner's case it has been isolated from the contents of the gall-bladder so long as eighteen years after recovery from the fever: also post-mortem it has been found in subjects many years after an attack of enteric fever. This predilection of *Bacillus typhosus* for the gall-bladder is supported by experiments performed on animals by Blachstein and Welch (1), who made intravenous injections of the organism into rabbits, and found it alive in the gall-bladder 128 days later, although it had completely disappeared from all other organs. There seems, therefore, no doubt that the bacillus is able to survive for a longer time in the gall-bladder than in any other part of the body, for nowhere else has it been found more than a few weeks after the fever has subsided: from the gall-bladder it can easily pass through the bile-duct into the small intestine, and so be thrown out in the faeces. It has been stated that normal bile is not a suitable medium for *Bacillus typhosus*,

but, as I have already said, it will grow in bile to a certain extent: now ox bile with the addition of a small percentage (2 per cent.) of peptone forms a very suitable and commonly used medium for the artificial growth of this organism. The probability is that during the first fourteen days of the fever the bacillus passes into the gall-bladder from the intestine, not directly but by way of the blood, for experiments on animals have shown that when a culture of the organism is injected into rabbits subcutaneously, intraperitoneally, or by the stomach, the bile always remains sterile, but when injected intravenously and after ligature of the common duct, the organisms can be found in large numbers in the gall-bladder. Having obtained an entry, the bacillus sets up an acute inflammation of the mucous membrane lining the gall-bladder and its ducts, with desquamation of the epithelium and exudation of albuminous material into the bile, thus rendering it a very favourable site for its growth and multiplication: in the majority of cases the inflammation subsides with the fever, but in a small percentage it subsists as a chronic cholecystitis, and these are the cases which become chronic typhoid carriers.

*The bacteriological examination of bile in one hundred and three cases.*

I have examined the contents of the gall-bladder in 103 cases—in 89 when removed from the body after death, and in the remaining 14 at the time of operation for cholelithiasis. In less than one-fourth of these cases was the bile sterile, and in both sets *Bacillus coli* was the organism most frequently found, sometimes associated with other organisms, but more often alone: other organisms occurring were *Bacillus proteus*, *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, and occasionally bacteria having no relation to the typhoid-coli group. On four occasions only were members of the typhoid-paratyphoid group isolated. I propose to deal first in detail with the 89 cases in which the bile was examined after death: these cases were all hospital patients, and the bile was examined irrespective of the cause of death, and it is noticeable that this appeared to have little or no connexion with the nature of the organisms present. The technique adopted was in all cases the same; the wall of the gall-bladder was sterilized over an area about two inches square by repeated applications of a red-hot flat-iron, and was then incised with sterile scissors, the bile and any gall-stones present being collected in a sterile test-tube, the mouth of which was immediately closed: at the same time a small quantity of blood was taken from the heart, from which the serum was afterwards obtained for agglutination reactions. The bile was then inoculated in fairly large quantities into broth, ox bile, or malachite green media, and on plates composed of MacConkey's or Conradi-Drigalski's medium, and incubated at 37° C., and if in twenty-four or forty-eight hours there was a growth of organisms likely to be of the typhoid-coli group, these were subcultured into the sugar media. Gall-stones were examined in the same way, the exterior being first sterilized and then the whole stone crushed and inoculated into the media.

Of the 89 cases examined in this way, in 20 the contents of the gall-bladder were sterile; in 47 *Bacillus coli* was isolated in pure culture; in 4 *Bacillus coli* was found associated with other organisms—twice with *Staphylococcus pyogenes aureus*, once with *Bacillus pyocyaneus*, and once with a diplococcus; in 6 cases *Bacillus proteus* alone was found; in 1 *Staphylococcus pyogenes aureus*, in 1 *Staphylococcus pyogenes albus*, in 1 a diplococcus, and in 7 bacilli having no relation to the typhoid-coli group. Gall-stones were present in only 5 of the above cases, and in 3 *Bacillus coli* was found, the other 2 being sterile. From the remaining 2 cases, details of which are given below, were isolated respectively *Bacillus paratyphosus* A and an organism which I was unable to classify.

The first of these was a boy aged 9 years, with a three weeks' history of headache and drowsiness; there was no family history of tuberculosis, and he was said never to have had typhoid fever. Examination of the cerebro-spinal fluid showed the presence of small lymphocytes, and on the symptoms and signs a diagnosis of tuberculous meningitis was made, and was fully confirmed at the autopsy. The liver and gall-bladder were normal, the bile black and viscid, and no organisms were seen in the freshly-stained specimen; it was inoculated into ox bile, and twenty-four hours later there was a growth of actively motile Gram-negative bacilli, which formed yellow colonies on MacConkey plates; these colonies were subcultured into the sugar media with the following results:—in dextrose, maltose, mannite, and dulcitate there was formation of acid and gas; litmus milk was permanently acidified, but not coagulated; lactose, cane-sugar, raffinose, salicin, and inulin were unaltered; gelatin was not liquefied; there was no fluorescence in neutral red broth and no indol production. The bacillus was agglutinated by the patient's own serum at a dilution of 1 in 100 in 30 minutes; a laboratory culture of *Bacillus paratyphosus* A was also agglutinated by the patient's serum at the same dilution in 30 minutes, but with a culture of *Bacillus paratyphosus* B there was no reaction. This case is of interest as the patient was only 9 years of age, there was no history of typhoid fever, and the only illness he had ever had was said to be measles, nor, so far as could be ascertained, had he recently been in the neighbourhood of persons suffering from typhoid fever, and yet *Bacillus paratyphosus* A was recovered in pure culture from the bile.

The second case was that of a man aged 49 with a two years' history of epigastric pain and vomiting, on whom the operation of gastro-enterostomy had been performed; there was no history of typhoid fever. The stomach was largely dilated and at the pyloric end was an old ulcer, and in both lungs there was extensive tuberculous disease with cavity formation; the liver and gall-bladder were normal and free from disease, there were no gall-stones present, but the bile contained a large number of motile Gram-negative bacilli, which formed yellow colonies on MacConkey's medium. These colonies were subcultured into the sugar media, with the result that dextrose and maltose were fermented with formation of acid and gas, in lactose there was acid formed but no gas, and



but, as I have already said, it will grow in bile to a certain extent: now ox bile with the addition of a small percentage (2 per cent.) of peptone forms a very suitable and commonly used medium for the artificial growth of this organism. The probability is that during the first fourteen days of the fever the bacillus passes into the gall-bladder from the intestine, not directly but by way of the blood, for experiments on animals have shown that when a culture of the organism is injected into rabbits subcutaneously, intraperitoneally, or by the stomach, the bile always remains sterile, but when injected intravenously and after ligation of the common duct, the organisms can be found in large numbers in the gall-bladder. Having obtained an entry, the bacillus sets up an acute inflammation of the mucous membrane lining the gall-bladder and its ducts, with desquamation of the epithelium and exudation of albuminous material into the bile, thus rendering it a very favourable site for its growth and multiplication: in the majority of cases the inflammation subsides with the fever, but in a small percentage it subsists as a chronic cholecystitis, and these are the cases which become chronic typhoid carriers.

*The bacteriological examination of bile in one hundred and three cases.*

I have examined the contents of the gall-bladder in 103 cases—in 89 when removed from the body after death, and in the remaining 14 at the time of operation for cholelithiasis. In less than one-fourth of these cases was the bile sterile, and in both sets *Bacillus coli* was the organism most frequently found, sometimes associated with other organisms, but more often alone: other organisms occurring were *Bacillus proteus*, *Staphylococcus pyogenes aureus*, and *albus*, *Streptococcus pyogenes*, and occasionally bacteria having no relation to the typhoid-coli group. On four occasions only were members of the typhoid-paratyphoid group isolated. I propose to deal first in detail with the 89 cases in which the bile was examined after death: these cases were all hospital patients, and the bile was examined irrespective of the cause of death, and it is noticeable that this appeared to have little or no connexion with the nature of the organisms present. The technique adopted was in all cases the same; the wall of the gall-bladder was sterilized over an area about two inches square by repeated applications of a red-hot flat-iron, and was then incised with sterile scissors, the bile and any gall-stones present being collected in a sterile test-tube, the mouth of which was immediately closed: at the same time a small quantity of blood was taken from the heart, from which the serum was afterwards obtained for agglutination reactions. The bile was then inoculated in fairly large quantities into broth, ox bile, or malachite green media, and on plates composed of MacConkey's or Conradi-Drigalski's medium, and incubated at 37° C., and if in twenty-four or forty-eight hours there was a growth of organisms likely to be of the typhoid-coli group, these were subcultured into the sugar media. Gall-stones were examined in the same way, the exterior being first sterilized and then the whole stone crushed and inoculated into the media.

stone was removed, the interior of which proved to be sterile; from the bile, however, was isolated in pure culture a motile, Gram-negative bacillus having the cultural characters of *B. typhosus*. The patient's serum also gave a good agglutination reaction with a laboratory culture of *Bacillus typhosus* at a dilution of 1 in 100: three weeks later *Bacillus typhosus* was again found in the bile, but at subsequent examinations only *Bacillus coli*.

The second case was a man aged 54, who for many years had been subject to attacks of biliary colic, but gave no history of typhoid fever. At the operation the gall-bladder was found to be chronically inflamed, thickened, and adherent, and contained a large quantity of pus but no gall-stones; from the pus was isolated an organism possessing the following characters:—it was rod-shaped and motile, but did not stain by Gram's method, and formed yellow colonies on MacConkey's medium, and in dextrose, maltose, mannite, and dulcitol it produced acid and gas; litmus milk was permanently acidified but not coagulated, and a green fluorescence was produced in neutral red broth; lactose, raffinose, and inulin were unchanged, and indol was not formed. The bacillus was agglutinated in 30 minutes at a dilution of 1 in 100 by the serum of a rabbit, which had previously given a positive reaction with *B. typhosus* at a dilution of 1 in 5,000, but unfortunately the other agglutination reactions were not performed. This organism, however, possessed the typical cultural reactions of *Bacillus paratyphosus A*.

Thirdly, a woman aged 29, who gave no history of typhoid fever, but had been subject to 'bad colds'; for nearly three years she had suffered from acute attacks of biliary colic. At the operation the liver and gall-bladder were both found to be enlarged, and the latter adherent and containing some small calculi and a quantity of dark-coloured pus, from which *Bacillus typhosus* was isolated in pure culture. The agglutination reactions in this case are of especial interest; the organism isolated was agglutinated at a dilution of 1 in 50 and partially at 1 in 100 by the patient's own serum, and at still higher dilutions by a stock laboratory typhoid serum, but a laboratory culture of *Bacillus typhosus* gave only a slight reaction with the patient's serum, there being no agglutination at dilutions greater than 1 in 20.

In 11 cases gall-stones were present, from 4 of which *Bacillus coli* was isolated in pure culture, the bile being sterile: of these 4 patients 3 were females and none of them were known to have had typhoid fever; but one, a woman aged 46, had nursed enteric patients in South Africa: at the operation the gall-bladder was found to be small and empty and only one gall-stone was present, lying in the common duct. The second patient, a woman aged 39, was the mother of five children and had suffered from bilious attacks as a child, but had never had any other illness; *B. coli* was again isolated, and was agglutinated by her serum at a dilution of 1 in 20, but at higher dilutions only partial clumps were formed at the end of an hour. Of the two other cases, one was a woman aged 52 and one a man aged 53, and both had for years been subject to attacks of biliary colic, and in both *Bacillus coli* was found.

Briefly summarized the contents of the gall-bladder were examined in 103 cases, with the following results:—

In 23 cases the contents were sterile.

In 51, one-half, *Bacillus coli* was isolated in pure culture.

In 4 *Bacillus coli* was found associated with other organisms, *Staphylococcus pyogenes aureus* twice, *B. pyocyaneus* once, and a diplococcus once.

In 6 cases *Bacillus proteus* was found, in 8 cases bacilli having no relation to the typhoid-coli group, and in 3 cases *Staphylococcus pyogenes aureus*: the following organisms were each isolated once:—*Staphylococcus pyogenes albus*, *Streptococcus pyogenes*, a diplococcus, and an unclassified bacillus. In 4 cases only were members of the typhoid-paratyphoid group found, these being *B. typhosus* twice and *B. paratyphosus A* twice.

Gall-stones were present in 16 cases, from which was grown in 7 cases *Bacillus coli*, in 1 *Staphylococcus pyogenes aureus*, and in 1 a bacillus not belonging to the typhoid-coli group: in the remaining 7 no organisms were found.

These results show that in a large proportion of cases organisms are present in the contents of the gall-bladder, whether examined during life or after death, even when the gall-bladder shows no evidence of disease, and in only about 22 or 23 per cent. is the bile sterile; on the other hand, the existence of pathological lesions in the bile passages does not of necessity mean infection of the bile, for out of 16 cases in which lesions were present it was sterile in 3, in one of which gall-stones were present. *Bacillus coli* is the organism most commonly found and was present in exactly one-half the cases examined; this result is in accordance with the findings of other investigators, the majority of whom have discovered *B. coli* in bile more often than any other organism; though generally alone, it may be associated with other bacteria, such as *Bacillus pyocyaneus* or the pyogenic cocci, and occasionally it presents very atypical features in its mode of growth. Pyogenic cocci were isolated both from bile and gall-stones in about 6 per cent. of the cases, and not infrequently bacilli having no relation to the typhoid-coli group, and these are not easy to identify, owing to the fact that certain organisms, such as the pneumococcus and *Bacillus tuberculosis*, can only be grown under special conditions and not on the ordinary nutrient media. *Bacillus proteus*, a putrefactive organism, which has been known to cause acute infection of the urinary tract, was isolated from about 6 per cent. The immediate cause of death appears to have little influence in determining the nature of the organism present in the gall-bladder, but, as would be expected, *Bacillus coli* is more frequently found when death is due to intra-abdominal disease than when it is due to affection of other parts. For instance, it was isolated in every case, except one, in which death was attributed to appendicitis or peritonitis, but was not once found when death was due to cardiac disease.

The causation of gall-stones is still a subject of discussion, and it is maintained by many that they are microbic in origin; but my results do not support

this opinion, for of 16 cases, in which gall-stones were present, they proved to be sterile in 8, *Bacillus coli* being isolated from 7, and *Staphylococcus pyogenes aureus* from 1. Naunyn too, amongst others, failed to find bacteria in newly-formed gall-stones. It cannot be disputed that certain organisms are able to exist for many years in the interior of gall-stones, but since these are so often sterile it must be doubted whether their formation can be directly attributed to the mechanical presence of bacteria; rather it would seem to be a secondary result of disease of the mucous membrane of the gall-bladder, set up by the invasion of such organisms.

In only 4 cases were bacilli of the typhoid-paratyphoid group isolated, and not one of the four was definitely known to have had enteric fever; it is, however, difficult to eliminate the possibility as the clinical symptoms vary so widely, and the explanation would appear to be that such patients have had at some time an attack of typhoid fever, but in a form so mild or so atypical that it escaped detection. However this may be, the fact clearly shows that persons, who have never been suspected of having had typhoid, are yet capable of harbouring in the bile-passages the specific organism of that complaint or one capable of producing symptoms very closely resembling it, and it is obvious that, once such an organism has established itself in this site, it can easily pass into the small intestine and be excreted in the faeces, whence infection of a new host may ensue: in other words, there are at large in the community individuals, never supposed to have had typhoid fever, who, unknown to themselves or any one else, are in reality chronic typhoid carriers. Semple and Greig (17) have shown, too, that persons in the immediate vicinity of typhoid patients are capable of acting in the same way, for after prolonged examination they isolated *Bacillus typhosus* from the faeces of 2 out of 4 enteric fever orderlies, none of whom had actually had enteric fever. It has been estimated that 3 to 4 per cent. of recovered typhoid patients become chronic carriers, and when we think of the large numbers who have recovered from this illness, and remember that there are in addition many others, in whom it has not been recognized or has pursued an abnormal course, we are able to realize to some extent the immensity of the problem which has to be faced in the endeavour to prevent the spread of typhoid fever.

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#### REFERENCES.

1. Blachstein and Welch, *Johns Hopkins Hosp. Bull.*, Baltimore, 1891, ii. 96, 121.
2. Charcot and Gombault, *Archives de physiol. norm. et path.*, 1876, 2nd ser., iii. 453.
3. Cushing, *Johns Hopkins Hosp. Bull.*, Baltimore, 1898, ix. 91.
4. Davies and Hall, *Proc. Roy. Soc. Med.*, Lond., 1908, i. 1, Epid. 175.
5. Dean, *Brit. Med. Journ.*, 1908, i. 562.
6. Dudgeon, 'Horace Dobell Lecture, 1908,' *Lancet*, Lond., 1908, ii. 1651.

7. Ehret and Stolz, quoted by Moynihan.
8. Forster and Kayser, quoted in *Brit. Med. Journ.*, 1908, i. 584.
9. Gilbert and Girode, *Compt. rend. Soc. biol.*, Paris, 1890, 9th ser., ii. 739; 1891, 9th ser., iii. 217.
10. Herter, *Medical News*, 1903.
11. Hewlett, *A Manual of Bacteriology*, Churchill, Lond., 1908.
12. Hunner, *Johns Hopkins Hosp. Bull.*, Baltimore, 1899, x. 163.
13. Ledingham, A. and J. C. G., *Brit. Med. Journ.*, 1908, i. 15.
14. Martha and Netter, *Arch. de physiol. norm. et path.*, 1866, 3rd ser., viii. 7.
15. Moynihan, *Gall-stones and their Surgical Treatment*, Saunders, Lond., 1905.
16. Naunyn, *A Treatise on Cholelithiasis*, 1892, transl. by A. E. Garrod, 1896.
17. Semple and Greig, *Scient. Mem. of Med. and Sanit. Off. Dept. Gov. of India*, Calcutta, 1908, xxxii.
18. Sherrington, *Journ. of Path. and Bacteriol.*, Edinb. and Lond., 1893, i. 258.
19. Terrier, *Rev. de Chir.*, Paris, 1893, xiii. 81.

# ON CARCINOMA ORIGINATING IN THE SUPRARENAL MEDULLA IN CHILDREN<sup>1</sup>

By R. S. FREW

With Plates 19-21

R. HUTCHISON, in 1907, was the first to draw attention to a 'definite "clinical syndrome" occasionally met with in children, consisting of cases of sarcoma of one or other suprarenal with metastases in the bones of the skull'. He brought forward ten cases in all, seven of which were published for the first time. He gave an excellent clinical picture of the disease, and one to which I have little to add, but in regard to the nature of the growth and mode of spread his observations were not so conclusive. He pointed out that whilst in the records they were usually described as small round-celled sarcomata, many of them may really have been 'malignant hypernephromata', which are more of the carcinomatous nature. He also drew attention to the fact that the metastases occurred mainly, and sometimes exclusively, in the bones, but thought there was no explanation to account for this. This paper was followed, in 1908, by one by Tileston and Wolbach, who published four new cases, one of which had come under their own observation, in addition to nine of those already recorded by Hutchison. They paid considerable attention to the pathological aspect of the disease, and regarded the growth as 'a small round-celled sarcoma belonging to the type in which these cells are supported by reticulum'. They summarized their observations as follows:—'The striking pathological feature is the finding of large identical tumours in the abdomen, involving only the adrenal, and in the cranium, involving only adjacent soft tissue and lymph glands. In spite of the frequent finding of tumour cells in the blood-vessels and lymphatics, metastases were found only in the bone-marrow, and the lymph nodes of the neck.' Rolleston, speaking of this disease, draws attention to the secondary metastases in bones as being comparable to the well-recognized association of carcinoma of the thyroid and skeletal metastases. In the latter class of case, however, von Recklinghausen maintains that the metastases occur through the blood-stream.

My own observations have convinced me that this disease gives rise to two

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entirely different 'clinical syndromes', and equally different pathological features according to which suprarenal has been the site of the primary growth. I propose, therefore, to discuss them separately, and as the symptoms and physical signs are best viewed in the light of the pathological changes, I shall discuss these first.

A. *When the Primary Growth is in the Left Suprarenal Medulla.*

I have made the autopsy on three cases of this class, and the appearances observed have been practically identical. The primary growth varied in size, the largest being as big as a cricket-ball, the smallest about the size of a walnut. It was round, had a mottled appearance, the groundwork being of an ivory colour, but numerous haemorrhages had occurred into it. Its consistency was firm and elastic for the most part, but where large haemorrhages had taken place it had a cystic feeling. It lay behind the peritoneum, in the usual position of the suprarenal, the left kidney being displaced downwards. In all my cases, and this has been noticed frequently in the other cases, a portion of the suprarenal cortex was seen closely applied to the tumour, usually lying at its upper and posterior part.

*Deposits in glands.* A mass of enlarged discrete glands was situated around the aorta at this level, the lumbar set, and this usually extended across the middle line. Several chains of enlarged glands ran from this:— (a) one downwards following the aorta to its bifurcation, and here dividing into two chains, which proceeded along the common iliac vessels, and further subdividing, passed along the internal and external iliacs on the two sides. These glands, and this is true of all the chains, were larger the nearer they were to the lumbar set, and gradually diminished in size as they became more distal. In none of my cases were the glands in the groin, or any beyond that, affected. (b) The mesenteric glands were much enlarged, the largest being near the attached border of the mesentery. (c) The gland at the hilum of the liver was involved in two of the cases, and in one of these a few deposits were found in the portal spaces. (d) A large chain passed upwards along the vertebral bodies behind the diaphragm, and through the posterior mediastinum. This lay in the position of the thoracic duct, and ended in a knot of glands behind the inner articulation of the left clavicle. (e) The anterior deep cervical set, on the two sides, was enlarged, that on the left side being largest in Cases 1 and 3, and that on the right side in Case 2. These passed upwards, along the carotid sheaths, and could be traced passing through the base of the skull, along with the internal carotid artery, whilst in one case a small gland was found in the wall of the cavernous sinus. (f) The glands running forwards in the intercostal spaces were involved; in Cases 2 and 3 all these glands on both sides of the chest were affected.

*Deposits in bones.* The deposits here are found in the medulla of the bones, 'the bone-marrow in children being always red marrow, and being closely allied

histologically and functionally to lymphadenoid tissue' (Hektoen). The bones involved in my cases were the cranial bones, the superior and inferior maxillae, the ribs and sternum, and in one case the iliac bones. The deposits here cause rounded subperiosteal swellings, both on the outer and inner tables of the skull, and in the case of the sphenoid there is a bulging forwards into the orbital cavity, thus causing the exophthalmos. On the inner aspect these protrusions push the dura mater in front of them, depressing the brain, and in one case causing thrombosis of a superficial cerebral vein. A point of great importance is that the cranial tumours and exophthalmos occur first on that side of the head on which the cervical glands are largest, and in the case of left suprarenal growths this is usually on the left side.

As regards the ribs, the swellings that occur take place on the inner aspect only, and are covered by periosteum. They are soft and resilient, and the effect produced is as if the bones were 'upholstered'. On section the outer compact layer appeared to be of the usual thickness, but the inner layer had been destroyed, its place being occupied by a soft, plum-coloured mass of new growth. In Cases 2 and 3 all the ribs were so affected, and all the intercostal glands on both sides were enlarged. In Case 1 only the sixth and seventh ribs on the right side and the seventh on the left side were 'upholstered', and the glands running along those spaces, and those glands only were enlarged. The sternum showed similar growth on its inner surface, usually most marked about the manubrium. In Case 1 the iliac bones were involved, the deposit being on the inner surface under the periosteum. No other secondary deposit, either in glands, bones, or other structures, could be found, after careful examination, in my cases.

In addition to these three, I have collected nineteen cases of this class, eight of them being taken from the records of the Hospital for Sick Children, Great Ormond Street, and eleven from the literature. Of these all with the exception of four cases (Cases 19, 20, 21, and 22) showed deposits in the cranial bones. In Case 19 there was a secondary growth in the third cervical vertebra only, whilst Cases 20, 21, and 22 showed no bone deposits at all, but in each instance there were deposits in the liver. It is interesting to note that those four comprise the youngest children in the whole series, death having occurred at the age of a few weeks, and it will be observed that the lymphatics involved are those nearest to the primary growth. The remaining fifteen cases are, almost without exception, very similar to those I have described. In all, the cranial bones were involved, the growths here being apparently similar in appearance and position to those found in my cases. In nine of the cases deposits in the ribs were found. Deposits in the liver were noted in four cases. As regards the glands affected, the description published was often of the briefest; still many indicate a condition similar to that observed in my cases, notably Cases 4, 15, and 17. Secondary deposits were found in a few new sites—in Case 8 the right ovary contained a deposit, whilst in Case 18 nodules are described as being present in the left arm and right leg, and a larger nodule in the right thigh, all



of which may have been glandular. In Case 16 the pericardium, left pleura, and lung were involved by direct extension.

*Clinical features.* Little can be added to Hutchison's picture of this disease, but I should like to draw attention to one or two of the early physical signs which were well shown in a case that was under observation practically from the beginning of the illness, and which have been recorded in a sufficient number of the other cases to warrant some importance being attached to them. This can best be illustrated, I think, by a brief reference to the case.

The child, a female, aged  $3\frac{1}{2}$  years, was brought with a complaint of pain in the left knee of two months' duration. She was a pale, well-nourished child, her temperature was  $100.6^{\circ}$ , there was some pain apparently on moving the left knee, the only other sign present being a loud apical systolic murmur. Dr. Garrod, under whose care the child was, and to whom I am indebted for permission to publish it, regarded the case as one of acute rheumatism. There was no improvement, however, under the usual treatment, and shortly after admission the glands at the angles of the jaw were noticed to be enlarged, those on the left side being the larger. Two weeks later a haemorrhage occurred into the left upper eyelid, and this was followed, on the next day, by one into the right eyelid. Dr. Garrod at once suggested what in the end proved to be the true nature of the disease, and from this time onwards an abdominal tumour was carefully sought for. Within a week there was definite optic neuritis in the left eye, the right being similarly affected later. One month after admission there was distinct proptosis, more marked on the left side, and a few days later a tumour was palpated in the left lumbar region, which gradually increased in size. About a week after this, the first cranial swelling was noticed, occurring at the left external orbital process, to be followed by many others. The cornea of the right eye ulcerated and sloughed, the child became blind, drowsy, and during the last few days was completely unconscious.

When one attempts to analyse the other cases, one finds that the clinical features have been stated so shortly in many of them, as to afford little information on these points, but in the eleven cases from the hospital records I have looked up these signs and symptoms: (a) Pain in the limbs was complained of in six cases, and of the remainder two were under two years of age. In four of the cases the pain was in the left lower limb, in one in both lower extremities, and in one in the right leg, and in this case a secondary deposit was present in the right tibia apparently, though it was not examined at the autopsy. I draw attention to this sign, because when the primary growth was in the right suprarenal, in no single instance was pain in the lower limbs complained of. I am therefore inclined to think it is caused by pressure of the enlarged glands on the lumbar plexus of nerves. (b) A systolic murmur on auscultation of the heart was noted in six of the eleven cases. This proportion is so much greater than when the primary growth is on the other side, that I think some importance must be attached to it. In no case was the heart enlarged, and the post-mortem examination showed the heart to be normal. It may perhaps be due to some compression of the great vessels by the enlarged glands in the posterior mediastinum. (c) Exophthalmos was present in fourteen of the twenty-two cases, and in eleven of those it occurred first on the left side. In one of the remaining three cases (Case 1) the glands on the left side of the

neck were much the larger on admission, and having been diagnosed as tuberculous, were removed. One week later proptosis appeared on the right side, to be followed in a few days by protrusion of the left eyeball. The importance of this sign becomes evident when we find that in the cases in which the primary growth was in the right suprarenal, in every instance the exophthalmos occurred first on the right side. (d) The blood was examined in eleven cases and showed a marked secondary anaemia, as observed by Hutchison. (e) Optic neuritis appears to have been a fairly constant sign. (f) The blood-pressure was taken in two of my cases and was normal, in one case being equivalent to 80 mm. of mercury, in the other to 78. (g) The temperature showed occasional slight rises, but as a rule was normal. In none of these cases was pigmentation noticed, nor was there any evidence of premature sexual development, such as Guthrie and Emery and Bulloeh and Sequeira have described in cases of carcinoma of the suprarenal cortex.

#### *B. When the Primary Growth is in the Right Suprarenal Medulla.*

The path of dissemination in this class is in the greater part of its course quite different from that found in the other class. But if the spread is by the lymphatic system, as I believe it is, and if the lymphatics from the right suprarenal join the right renal lymphatics, and communicate with the lumbar set of glands, as occurs in the case of the left suprarenal, then we should expect the appearances to be similar in the two classes of cases—but they are not! How then is this to be accounted for? The explanation, I think, lies in the fact that whereas the lymphatics from the left suprarenal run to the lumbar glands, those from the right suprarenal are tributaries of the right lymphatic trunk. In favour of this view are the observations made in cases where the disease starts in the right suprarenal; and in addition there is a considerable amount of anatomical evidence to support it. It will be remembered that the hilum of the suprarenal differs in position on the two sides, for whereas on the left side the vein passes out at the lower end of the inner border to join the left renal vein, and the lymphatics accompany it, on the right side the vein passes out at the upper end of the internal border and runs to join the inferior vena cava. Moreover, this portion of the right suprarenal is uncovered by peritoneum and is closely applied to the 'bare area' of the right lobe of the liver, and it is just this portion of the liver which is generally stated to be drained by the tributaries of the right lymphatic trunk.

I have collected twenty-nine cases in which the primary growth has been apparently in the right suprarenal medulla, thirteen of them being taken from the hospital records: and on two of these I performed the autopsy. The primary growth in this class, whilst very similar in most respects to that found on the left side, is usually much larger, and more frequently remains localized to the abdomen, this occurring in twelve cases. Further, the primary growth tends to involve the kidneys by direct extension into their pelves, stretching out the

kidney substance over it, but being easily separated as a rule. In eleven cases this extension had taken place into the right kidney, in two into the left kidney, and in one into both.

*Deposits in glands.* (a) On the upper surface of the liver, small flattened-out chains may be seen running in under the peritoneal coat, the largest glands being those nearest to the bare area. (b) On the upper surface of the right side of the diaphragm, a chain is seen under the pleura, and this runs inwards to the anterior part of the pericardium, where it passes upwards in the anterior mediastinum to terminate in a knot of glands behind the inner end of the right clavicle. (c) The glands at the root of both lungs are involved, and also those passing into both lungs. The above were all well shown in my case (Case 29). In six of the cases I have collected the spread had gone still further, the anterior deep cervical glands being affected, especially those on the right side, and in every instance proptosis had first appeared on the right side.

*Other deposits.* I have already mentioned the deposits on the surface of the liver, which are different to those noticed in Class A, the deposits there being in the portal spaces. The deposits in the lungs were obviously lymphatic, being found either immediately under the pleura, or else alongside a bronchus. It is worthy of note that both lungs as a rule were affected. Similar deposits have been recorded in the cases I have collected. In twenty of the twenty-nine cases deposits in the liver were found. The lungs showed metastases in nine out of sixteen cases in which deposits above the diaphragm had occurred. Special interest attaches to these deposits, as when the primary growth was in the left suprarenal the lungs were never involved. In the six cases in which extension to the cranium had occurred the appearances were similar to those found in the majority of the cases in Class A. In only one case were the ribs affected, and the growth here is described as being at the costo-chondral junction—thus differing from the position of the growths in the ribs in Class A.

*Clinical features.* These are not so distinctive as those recorded in Class A. (a) Pain was complained of in thirteen of the cases, and it was referred to the abdomen in every case, and never to the limbs. (b) The primary growth is easily palpable in these cases owing to its large size, though in the early stages the liver may be tilted forward, thus rendering the palpation difficult. (c) The examination of the blood gave again evidence of marked secondary anaemia. (d) The blood pressure was taken in Case 29, and was equivalent to 98 mm. of mercury. (e) Exophthalmos, when it did occur, was always on the right side first. (f) The mass of glands behind the inner end of the right clavicle is usually easily palpable.

The clinical features and the pathological findings in the two classes thus present a very different picture, and these differences, which are so constant, would be impossible to explain, I think, on the assumption of a blood spread. But if, as it appears to me, the secondary deposits are but extensions of the primary growths along the lymphatic channels, it would at one and the same time explain the constancy of the metastases in certain groups in each class,

and also the difference between those groups in the two classes. The dissemination is not always in the direction of the lymph stream, but backward transport along the lymphatic channels takes place almost as readily in such cases, as shown by Handley and others.

*Nature of the growths.* I have examined sections from seven cases (Cases 1, 2, 3, 4, 23, 29, and 30) and the appearances in all are very similar. The cells are round or oval in shape, about  $6\mu$  in diameter, and appear to be made up chiefly of nucleus. The protoplasm is granular. There is a delicate supporting framework of long narrow cells with spindle-shaped nuclei, the round cells being arranged in clumps in the spaces. The growth is surrounded by a thick fibrous capsule, from which coarse trabeculae pass inwards, the finer fibres arising from these. Extravasation of red blood corpuscles into many of the spaces is seen. Some formed blood-vessels are present in the different sections. In Case 4 a portion of unaffected cortex was present in the same section as the new growth. The secondary deposits show the same characters. The appearance is thus quite different from that described by Bulloch and Sequeira in their case of carcinoma of the suprarenal cortex, in which the tumour had almost exactly reproduced the zona fascicularis of the cortex. As a rule the growths of the medulla have been described as a small round-celled sarcoma, but many authorities have stated at the same time that they do not consider the classification entirely satisfactory.

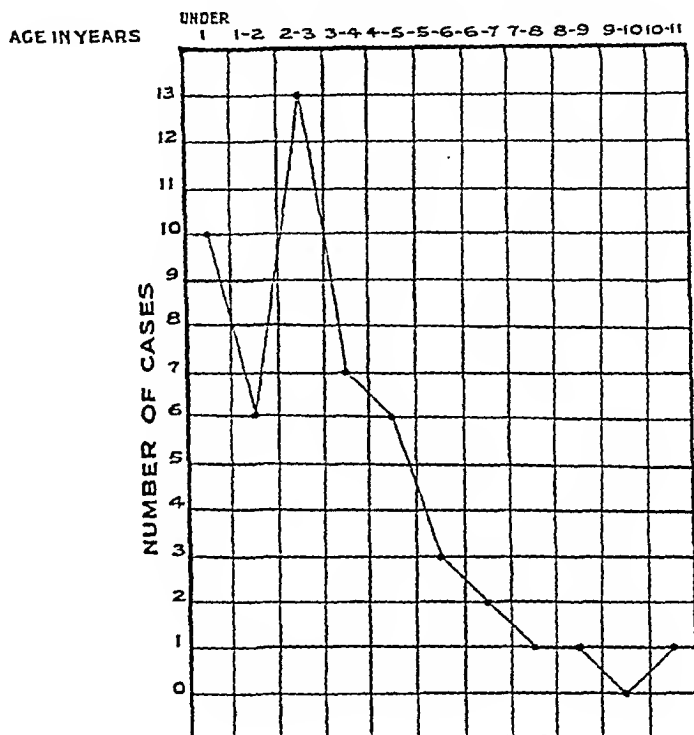
Rolleston, speaking in this connexion, says, 'The primary malignant growths of the medulla are histologically more allied to gliosarcoma than to carcinoma. It is obvious that these tumours form a special group, and it is probably most convenient to describe them simply as malignant hypernephroma.' Again, Hutchison says of one of his cases: 'There was certainly some doubt whether the tumour should be classed as a sarcoma or as a papilloma.' Aisenstein classifies his as an endothelioma belonging to the hypernephroma group, whilst Professor Welch, who examined the tumour in Case 48, says, 'Not certainly sarcoma,' but he is inclined to regard it as such. The suprarenal medulla we know is neuro-ectodermal in origin, and therefore malignant growths arising here are more likely to be carcinomatous; moreover, its mode of spread being by the lymphatic system, I regard the growth as being more closely allied to a carcinoma, than to a sarcoma.

### *Etiology.*

The youngest case I have been able to find was two weeks of age, the oldest ten years. The age incidence (based on the age at which death occurred) shows that the largest number of cases occurred between the ages of two and three years. By far the greatest number of cases occurred before the age of six. In this series of cases there were twenty-seven males to nineteen females. (In five cases the sex was not stated.) *Heredity* seems to play no part. In not a single case was there evidence of anything similar having occurred in the family.

Trauma has been supposed to be the cause in several of the cases, but it is of such frequent occurrence in children that I think no importance can be attached to it. The hospital records comprise about 7,000 autopsies on children under twelve years of age, and of these twenty-five were cases of this disease.

CHART SHOWING AGE INCIDENCE



### *Diagnosis.*

It has been pointed out already, how the left-sided cases may in the early stages simulate rheumatism, but the further development of the disease soon clears up the diagnosis. Hutchison has drawn attention to the ecchymoses into the eyelids seen in chloroma and in infantile scurvy being confused with this disease, and also how they may be differentiated. Case 1 in my series was thought to be a case of cavernous sinus thrombosis secondary to operation on glands in the neck, and in young infants, where the whole duration of the disease is so short, the diseases may appear very similar—the palpation of the abdominal tumour, however, would distinguish them. As regards the cases occurring on the right side, when they come under observation early the abdominal tumour may be impossible to diagnose from a renal sarcoma, the more so as the kidney may be involved in the growth.

*Prognosis.*

This disease invariably proves fatal. As a rule, the younger the patient the shorter its duration. The tables show cases lasting from twelve days to eighteen months. Operation seems to offer little hope of success, for the diagnosis is not usually made until secondary growths have occurred.

In conclusion I desire to express my thanks to Drs. Garrod, Voelcker, and Colman for permission to make use of cases under their care.

*Conclusions.*

1. That carcinoma of the suprarenal medulla spreads by the lymphatic system, and gives rise to different appearances, according as the left or right suprarenal is primarily affected.

2. That on the left side, secondary deposits occur in the liver, in the ribs and cranial bones, and in the thoracic duct and certain of its tributaries.

3. That on the right side, secondary deposits are found on the upper surface of the liver, in both lungs, and, in a few cases, in the cranial bones, and also in the right lymphatic trunk and certain of its tributaries.

4. That all the structures above mentioned are affected through their lymphatic vessels, and that all the cases described can be classified under these two groups.

#### CLASS A. CASES IN WHICH THE PRIMARY GROWTH WAS IN THE LEFT SUPRARENAL MEDULLA.

Case 1 (P. M. Records, vol. xxiii, no. 131<sup>1</sup>). M. 1½. Duration: About 6 weeks. Clinical course: Two weeks before admission glands noticed enlarged on L. side of neck. On admission—large mass of glands at lower part of L. side of neck. These were removed nine days later. Four days afterwards proptosis of R. eye developed, and a week after this exophthalmos of L. eye. Death occurred three weeks after operation. Primary growth: Large plum-coloured growth involving L. suprarenal medulla, a portion of the cortex being spread over it like a hood. 'Cells with large round nuclei and small amount of protoplasm.' Bones: Small nodule over R. external orbital process. Whole of inner surface of calvarium covered with small nodules of new growth lying under dura. Growths in sphenoid, projecting from lesser wings into orbits. Growths at both angles of lower jaw. The ribs involved were R. 6th and 7th and the L. 7th. Inner surface of both iliac bones also showed subperiosteal growths. Glands: Lumbar glands greatly enlarged: from this a chain ran downwards and along both common iliacs and both external and internal iliacs, gradually becoming smaller as they descended. Another chain passed upwards through posterior mediastinum, ending in a large mass behind inner end of L. clavicle, from which two chains ran upwards along carotid sheaths and could be traced entering skull with internal carotid arteries. Mesenteric glands involved, also gland at hilum of liver.

<sup>1</sup> Hospital for Sick Children, Great Ormond Street.

Case 2 (P. M. Records, vol. xxii, no. 224). F. 2 years. Duration: About 6 weeks. Clinical course: Pale and irritable for one month before admission. Ecchymoses into lids of both eyes, R. first, then swellings on R. temple, and proptosis of R. eyeball. On admission—small lumps also found above L. ear. Large tumour in L. lumbar region. Had pain in L. ankle. Loud systolic murmur at apex. Double optic neuritis. Urine normal. R. cornea ulcerated towards end. Marked exophthalmos on both sides. Primary growth: Large tumour of L. suprarenal, soft, reddish brown in colour. 'Cells with large round nuclei and small amount of protoplasm.' Bones: Several rounded nodules on calvarium, chiefly on R. side, some causing bulging of dura mater, and one over R. frontal lobe had perforated it and depressed brain substance. Growths also in R. lesser wing and body of sphenoid. Growths in both orbits—R. more marked. Deposits in superior and inferior maxillae. All ribs showed growths along inner aspect under periosteum. Glands: One chain of large glands ran upwards through posterior mediastinum to behind the inner end of L. clavicle and dividing into two sets passed upwards to the carotid foramina—more marked on R. side. Another set passed along with portal vessels to the liver hilum. Still another went along iliac vessels, and continued along external iliac on L., internal iliac on R. side. Lastly a set along anterior edge of diaphragm—more marked on L. side. Mesenteric glands slightly enlarged. Other deposits: The liver had a mottled red and brown surface. Blood examination: Red cells 2,040,000. Hb. 40 %. White cells 6,500. Polymorphs 38 %. Lymphocytes 56 %.

Case 3 (P. M. Records, vol. xxii, no. 66). F. 3½ years. Duration: 6 months. Clinical course: Complained of pain in back and L. leg. On admission—apical systolic murmur. Later—glands at angles of jaw enlarged, especially on L. side. Then ecchymosis into L. upper eyelid and proptosis of L. eyeball. Double optic neuritis. One month later tumour felt in L. lumbar region. Swellings on cranium appeared, first on L. side, then all over. Exophthalmos of both eyes. R. cornea ulcerated. Primary growth: Large firm elastic growth in L. suprarenal. 'Cells with large rounded nuclei and small amount of protoplasm.' Bones: About twenty distinct tumours on outer aspect of calvarium, largest over L. parietal bone, and this one caused some bulging of inner table, and underlying superficial cerebral veins were thrombosed. Growths from sphenoid projecting into orbits. All the ribs, and lower part of manubrium sterni, showed growths on inner surface under periosteum. Glands: Continuous chain of glands from pelvis to carotid foramina, single in thorax (posterior mediastinal), double in abdomen and neck. Smaller chain running from L. suprarenal growth joined the main chain at the lumbar glands. Blood examination: Red cells 2,480,000. Hb. 47 %. White cells 10,250. Polymorphs 36 %. Lymphocytes 59 %.

Case 4 (P. M. Records, vol. xx, no. 55). (Cited by Hutchison.) F. 4 years. Duration: 9 months. Clinical course: Brought up with pains in arms, legs, and head. On admission—tumour felt in L. lumbar region. Glands in neck enlarged, especially on R. side, also in both groins. Optic neuritis. Later, lumps appeared on head, first over R. temple. Proptosis of both eyes—L. first. Gland and swellings increased in size. Systolic murmur at apex. Primary growth: L. adrenal occupied by large, hard, white growth, with an unaffected portion still adherent to it. 'Small round and oval-celled sarcoma.' Bones: About twelve growths over cranium. These growths were also seen on inner surface, bulging dura, but not invading it. All ribs, except first pair, showed subperiosteal growths along inner surface. Glands: Glands under angles of jaw infiltrated, also posterior cervical glands, and a chain through thorax to abdomen. Glands also involved in both groins and both axillae. Blood examination: Red cells 3,942,000. Hb. 70 %. White cells 10,500. Polymorphs 51 %. Lymphocytes 44 %.

Case 5 (P. M. Records, vol. xvi, no. 204). (Cited by Hutchison.) M. 10 months. Duration: 3 weeks. Clinical course: Swelling first appeared on L. side of head, followed by two others on top of head. On admission—a large tense elastic swelling, size of half an orange, in L. temporal fossa. Later, L. eye became proptosed, and haemorrhage into L. upper eyelid. More swellings appeared over head. Primary growth: Tumour lay between L. kidney and suprarenal, the latter being spread over it like a hood, and continuous with it internally. 'Sarcoma.' Bones: Large tumour over L. temporal, parietal, and frontal bones. Internally it bulged the dura mater, but did not perforate it. Several other smaller growths on calvarium. Glands: Cervical glands on either side were infiltrated with growth. A small affected gland

lay between L. suprarenal and aorta. Blood examination: Red cells 3,125,000. White cells 12,000.

Case 6 (P. M. Records, vol. xv, no. 327). F.  $7\frac{1}{2}$  years. Duration: 4 months. Clinical course: History of lameness in R. leg for two months, and wasting during that time. Vomiting frequently. On admission—firm, discrete glands on both sides of neck, more marked on L. side. Soft, projecting tumour over occiput. Large nodular tumour felt in L. lumbar region. Urine contained trace of albumin. Later, developed optic neuritis. Primary growth: Large tumour ( $4\frac{1}{2}$  lb.) surrounding and involving the L. suprarenal. 'Small round-celled sarcoma.' Bones: Large soft purplish tumour on L. side of occipital bone, bulging dura greatly, but not invading it. Growth on outer side of L. orbit. Growth on inner surface of 5th rib, projecting into pleura. Glands: Retroperitoneal mesenteric, R. iliac, and lower L. tracheal glands involved, also those at hila of kidney and liver. Other deposits: Growth into L. kidney from hilum. Growths in both ovaries. Small diffuse growths in liver. Blood examination: Red cells 2,260,000. Hb. 50 %. White cells 5,000.

Case 7 (P. M. Records, vol. viii, no. 57). (Cited by Hutchison.) M.  $8\frac{1}{2}$  years. Duration: ? 10 months. Clinical course: Six months before admission struck by stone on forehead; since that headache, nausea, and vomiting. Ecchymosis of L. eye since injury, R. eye became black later. On admission—tumour in L. lumbar region. L. cervical glands enlarged. Urine normal. Later, tumours appeared at external orbital angles on both sides. Both eyes became proptosed—L. first. Optic neuritis. Cornea on both sides ulcerated. Swellings on R. tibia, lower jaw, and malar bones. Primary growth: Large, soft, variegated mass, occupying L. side of abdomen, involving L. kidney and suprarenals. 'Sarcoma.' Bones: Large, soft, reddish tumours in both temporal regions, over L. parietal region, and at root of nose, also into both orbits. Areas of growth between dura and skull, and dura and brain, but not invading brain substance, though it had caused yellow softening in L. temporo-sphenoidal lobe by pressure. Glands: Mesenteric glands of dark red colour, but not obviously enlarged. Blood examination: 1 white cell to  $23\frac{1}{2}$  red cells.

Case 8 (P. M. Records, vol. vi, no. 251). (Cited by Chaffey.) F. 3 years. Duration: ? 8 months. Clinical course: Had been getting pale and languid, and then lumps appeared on head. Difficulty in walking for three months, and in passing urine for one month. On admission—lower extremities wasted. Small swelling to R. of spine of last lumbar vertebra. Swellings in scalp in temporal and parietal regions. Systolic murmur over praeecordium. Primary growth: L. suprarenal involved, with rim of normal tissue. 'Round-celled sarcoma.' Bones: Large tumour in R. parietal bone, causing swelling equally on both surfaces. Similar smaller one on L. side. Dura was pushed before them. Swellings on posterior aspect of manubrium sterni, and on inner aspect of all the ribs. Subperiosteal growths on dorsum ilei. Glands: Numerous large retroperitoneal glands, some pushing through the intervertebral arches in the lumbar and sacral regions and pressing on the spinal theca, though not invading it. One at lower part of L. side of neck. Mesenteric glands normal. Other deposits: Growth in R. ovary; L. kidney contained numerous small deposits in cortex resembling tubercles and pus in the pelvis.

Case 9 (P. M. Records, vol. iv, no. 260). F.  $3\frac{1}{2}$  years. Duration: About 7 months. Clinical course: Commenced with pain in abdomen and back and cramp in L. leg. Eyelids swollen later. Swellings appeared on head. On admission—small swelling over R. parietal region. Glands on L. side of neck enlarged. Tumour felt in L. iliac fossa. Later, double optic neuritis. L. eyelid swollen. Swellings appeared on L. side of head. Systolic murmur loudest at apex. Primary growth: In L. lumbar region beneath suprarenal is found a greyish-white firm body size of walnut. Bones: Large soft purplish swelling over both parietal bones, also many other smaller ones. One over internal occipital protuberance has dura mater adherent. Numerous soft growths along base of skull and in both orbits, especially in L. Inner surface of all ribs and second piece of sternum show irregular purple swellings. Glands: In R. iliac fossa, lying against bones of pelvis, is a large, soft, purple gland. On the L. side a chain of glands runs from brim of pelvis to level of 2nd lumbar vertebra, each containing new growth. Blood examination: Red cells diminished. White cells show no increase.

Case 10 (P. M. Records, vol. iii, no. 165). M. 5 years. Duration: ? 7 months. Clinical course: Frontal headache for seven months. About one month ago R. arm and leg became



paralysed—arm gradually recovered, but he is not yet able to walk. Six weeks ago L. side of chest began to bulge. Eyes swollen for one month and head is getting larger. On admission—proptosis on both sides, L. more marked. Double optic neuritis. Systolic murmur at apex. Urine normal. Primary growth: Not clearly indicated, but apparently 'about kidneys'. 'Cancer.' Bones: Cranium very soft, inner surface covered with spicules of bone, some of which adhered to dura. Growth in L. orbit. Cancerous mass on posterior surface of sternum and on inner surface of 2nd and 3rd L. ribs. Glands: Mesenteric glands enlarged and congested, some caseous. Bronchial glands a little large and congested. Other deposits: Cancerous material scattered through liver, apparently round the interlobular veins. Kidneys much enlarged, mottled red and white. Blood examination: White cells showed no increase.

Case 11 (P. M. Record, vol. ii, no. 295). M. 10 years. Duration: 13 months. Clinical course: Eight months before admission fell against a chair, injuring his L. side. Occasional shooting pains in L. thigh. Three months ago tumour felt in L. lumbar region. Two months after admission L. leg became paralysed. Later, lumps appeared over L. eyebrow and in L. occipital region. Swelling and redness of L. eyelid. No optic neuritis. Primary growth: Large mass in abdomen, 'apparently starting in glands in L. lumbar region.' Bones: Two large lumps on calvarium—one frontal, the other occipital—bulging dura, but not perforating it. Growth in L. orbital cavity. Glands: Lumbar glands affected. Blood examination: Blood appeared normal.

Case 12 (Hutchison, Case V). M.  $2\frac{1}{2}$  years. Duration: Not stated. Clinical course: Fall on head three weeks before admission. Swelling of eyes and face started afterwards. Both eyes proptosed. Ecchymoses of lids. Growths in temporal fossae and swelling felt in L. hypochondrium. Primary growth: Sarcoma of L. suprarenal. Bones: Calvarium infiltrated with new growth. Other deposits: Small nodule in liver. Blood examination: Red cells 3,200,000. White cells 8,400. Polymorphs 47%.

Case 13 (Hutchison, Case VI). M. 3 years. Duration: About 11 weeks. Clinical course: Ill for two months, but getting pale for a considerable time. Profoundly anaemic. Haemorrhage from gums. Growth appeared in L. temporal fossa. Slight proptosis of L. eye. Optic neuritis. Blindness. No tumour felt in abdomen. Urine normal. Primary growth: Sarcoma of medullary part of L. suprarenal. Bones: Infiltration of calvarium and of thoracic spinal column. Blood examination: Red cells 1,400,000. Hb. 38%. White cells 8,000. Polymorphs 65%.

Case 14 (Hutchison, Case X). M. 3 years. Duration: About 8 weeks. Clinical course: Blacking of L. eye noticed four weeks ago. On admission—both upper lids blackish (? haemorrhagic). Haemorrhages into L. conjunctiva. Ovoid elastic tumour over R. parietal eminence. Rounded prominence just above R. ear (? haematoma). Profoundly anaemic. Spleen palpable. Urine normal. Later, his abdomen became tender, but no definite tumour was felt. Primary growth: Large mass above L. kidney which was easily separated from surrounding tissues. No evidence of a suprarenal capsule. 'Lymphosarcoma.' Bones: Entire surface of skull covered by large masses of new growth, which was for the most part soft on section, but contained some spicules of bone. The growth invaded both orbits, but not the cavernous sinuses. Glands: Neighbouring glands enlarged by infiltration. No enlargement of mediastinal glands.

Case 15 (Aisenstein). M. 2 years. Duration: About 14 weeks. Clinical course: Complaining of anaemia, wasting, and pain on standing or walking. Fullness in chest due to mediastinal glands. Albumin in urine. One month later had haemorrhage into L. eyelid. Haemorrhagic pleural effusion. Lateral displacement of lower dorsal vertebrae. Finally large tumour on frontal bone, large deep-seated mass in region of stomach, with small scattered round tumours in abdomen. Primary growth: Large tumour of L. adrenal. 'Endothelioma.' Bones: Numerous metastases to skull and ribs. Glands: Metastases to abdominal and cervical glands. Other deposits: Extension to pancreas.

Case 16 (Mann). Sex? 2 years. Duration: 14 weeks. Clinical course: Complaint of weakness, pallor, and abdominal pain. Cervical glands enlarged. Later, a large tumour (apparently splenic) palpable in abdomen. Proptosis of L. eye, and haemorrhage into cellular tissue of L. orbit. Subcutaneous haemorrhages over sternum and scalp. L.-sided pleural

effusion. No pigmentation. **Primary growth:** Large tumour of L. suprarenal ( $7'' \times 4\frac{1}{2}''$ ). Kidney at lower pole surrounded but not invaded. 'Round-celled sarcoma.' **Bones:** Secondary deposits in both orbital plates of frontal bone, in the R. parietal bone, and in the sternum. **Glands:** Cervical glands were sarcomatous. Few glands near hilum of L. kidney involved in growth. **Other deposits:** Direct invasions of pericardium and L. lung by growth. L. pleural cavity contained nearly a pint of blood-stained fluid and small secondary growths on internal surface of parietal pleura. **Blood examination:** Hb. and red cells 60 %. White cells 15,000. Polymorphs 55 %. Lymphocytes 40 %.

Case 17 (Targett). M. 1 year. **Duration:** 11 weeks. **Clinical course:** Fell out of chair two months ago and soon afterwards swelling appeared in L. frontal region. On admission there was a hemispherical swelling here 3'' in diameter. Later, two other smaller tumours appeared on head. All grew rapidly. **Primary growth:** Large mass of growth surrounded a healthy L. kidney. L. ureter passed through the mass, and pelvis of kidney was dilated. 'Round-celled sarcoma.' **Bones:** Large dark-red soft growth in L. side frontal bone—bulging dura, but not adherent. Several smaller deposits in neighbourhood. Another in L. lesser wing of sphenoid, and a much larger one on L. temporal fossa. Several ribs on both sides invaded at sternal ends, and sternum itself was almost entirely replaced by growth. **Glands:** Large mass of growth along dorsal spine, but not invading vertebrae. Below, this was continuous with similar mass in abdomen which reached the whole length of the lumbar spine, and on the L. side to spleen, tail of pancreas, and kidney.

Case 18 (Richards). M. 6 months. **Duration:** 4 months. **Clinical course:** When two months old, swelling appeared on posterior fontanelle, and had grown to size of orange—soft and fluctuant. Other lumps had since appeared on head, and some on legs. One mass had destroyed the R. eye. **Primary growth:** Both suprarenals destroyed by soft vascular growths; L. more prominent. 'Small round-celled vascular sarcoma.' **Bones:** Three tumours on calvarium—one occipital, one on each half of frontal—soft and full of blood. Dura mater free. Ribs 5 and 6 showed new growth. **Glands:** Growth in posterior bronchial glands. Mesenteric glands a little enlarged. **Other deposits:** Patches in liver. Nodule in subcutaneous tissue of L. arm and R. leg. Larger nodule on R. thigh with periosteal base.

Case 19 (Caillé). Infant. **Duration:** ?. **Clinical course:** Moribund when seen. **Primary growth:** Tumour of L. suprarenal. 'Round-celled sarcoma (cystic).' **Bones:** Diffuse growth in 3rd cervical vertebra.

Case 20 (Richards). M. 2 weeks. **Duration:** 12 days. **Clinical course:** Abdomen noticed to be swollen two days after birth, and it had got bigger since. Oedema of legs, abdomen, and back. Urine normal. **Primary growth:** Large tumour in L. adrenal with normal cortex surrounding it. 'Small round-celled vascular sarcoma.' **Glands:** Glands in portal fissure infiltrated. **Other deposits:** Liver much enlarged, mottled yellow. Infiltrated throughout with new growth.

Case 21 (Dalton). M. 6 weeks. **Duration:** 6 weeks. **Clinical course:** At birth abdomen was noticed to be large. Hard swelling in abdomen. Liver below umbilicus. **Primary growth:** Tumour, size of hen's egg, in L. adrenal. Small portions of cortex seen unaffected. 'Small round cells—striking resemblance to carcinoma.' **Other deposits:** Liver, weight  $37\frac{1}{2}$  oz. Numerous haemorrhages and areas of new growth on surface and in substance.

Case 22 (Parker). Sex? 5 weeks. **Duration:** 2 weeks. **Clinical course:** When three weeks old, swelling and hardness of abdomen were noticed. No jaundice. On palpation, tumour began in liver region and reached quite over to opposite side, and as low as iliac crests. Slight oedema of lower extremities. **Primary growth:** Between L. kidney and spleen was a mass of new growth as large as a Tangerine orange, and it invaded neither organ. 'Round-celled sarcoma.' **Other deposits:** Liver, 23 oz. Nodules of new growth over surface and throughout entire organ, varying in size from millet-seed to walnut.

### CLASS B. CASES IN WHICH THE PRIMARY GROWTH WAS IN THE RIGHT SUPRARENAL MEDULLA.

Case 23 (P. M. Records, Hosp. for Sick Children, Gt. Ormond St., vol. xxx, no. 60). M.  $2\frac{1}{2}$  years. Duration: About 6 months. Clinical course: Lumps on head noticed five months before admission—getting larger. Swellings on R. side of forehead, and in L. temporal fossa. Enlarged glands in suboccipital and around mastoid regions. Had systolic murmur over praecordium. Later developed ecchymosis of R. upper and lower eyelids. Primary growth: R. adrenal contained new growth, size of shelled walnut, with fringe of apparently normal adrenal. Round and oval-celled sarcoma. Bones: Numerous soft, red, spongy masses on calvarium, bulging dura, but not perforating it. Growths in basi-sphenoid and in both orbits. Glands: Large on both sides of neck, especially on R. side. Large gland near pelvis of R. kidney. Other deposits: Few secondary nodules in liver. Blood examination: Red cells 1,572,000. Hb. 45 %. White cells 14,000. Polymorphs 39 %. Lymphocytes 55 %.

Case 24 (MacCarty). Sex ?  $2\frac{1}{2}$  years. Duration: ? 10 months. Clinical course: Eight weeks before admission small swelling L. side of head. Soon afterwards R. exophthalmos, enlarged gland behind ear and in L. axilla. Small tumours in jaw, in L. parietal region, and in L. axilla. Primary growth: Tumour in R. adrenal size of child's head. Malignant hypernephroma. Bones: Four metastases in cranium. Glands: Metastases in axilla. Blood examination: Polymorphs 70 %. Lymphocytes 27 %. Eosinophiles 3 %. No nucleated reds.

Case 25 (Tileston and Wolbach). M. 16 months. Duration: About 7 weeks. Clinical course: One month before admission purple discoloration of R. upper and lower eyelids. Later, exophthalmos of R. eye. Soft mass over R. temporal region. Nothing felt in abdomen. R. preauricular glands and those at angle of jaw considerably enlarged. Finally ecchymosis appeared in R. lower eyelid. Primary growth: Soft, elastic, and irregular tumour of R. adrenal. Small round-celled sarcoma. Bones: Large tumour on R. side of skull. Ribs and other bones normal. Glands: Enlarged glands at R. side of neck, at angle of jaw, and along sternomastoid. Other deposits: Pelves of both kidneys much dilated and contained numerous soft brown masses of granular material.

Case 26 (Bruck). F. 14 months. Duration: About 3 weeks. Clinical course: Pain and swelling in abdomen for two weeks. Discoloration and swelling of R. eyelid. Tumour palpated on R. side of abdomen, reaching nearly to anterior superior spine of ilium. Operation. Death. Primary growth: Large tumour of R. adrenal. Small round-celled sarcoma. Bones: Growths on cranial roof. Small tumour on upper wall of orbit, and in the dura of the frontal bone. Glands: Metastases in mesenteric and prevertebral glands. Other deposits: Tumour in liver. Pancreas involved by extension. Some consolidation of R. lower lobe.

Case 27 (Cohn). F. 9 months. Duration: 5 weeks. Clinical course: Brought for swelling on R. temple and protrusion of R. eyeball. Behind L. ear were five smaller tumours. Tumour felt deep in R. flank. Rapid growth of abdominal and cranial tumours. Great enlargement of occipital and deep cervical glands. Primary growth: Large tumour in R. adrenal. Medullary sarcoma, primary in R. adrenal (Virchow). Bones: Numerous growths in skull, also in most of the ribs at their costo-chondral junctions, and they were thickened along the whole extent of their inner periosteal coat. Glands: Cervical and occipital glands involved. Mesenteric glands slightly enlarged. Other deposits: In liver, in R. kidney, and in L. ovary.

Case 28 (Ogden and Matthews). M. 5 years. Duration: About 6 weeks. Clinical course: Slight fall six weeks before admission. Three weeks later, severe pain in back; one week later, discoloration of eyelids. Swellings on head. Large tumour in R. flank. Liver down to umbilicus. Glands in neck palpable. Optic neuritis. Progressive anaemia. Rupture of cornea. Marked double proptosis. Primary growth: Large mass of retroperitoneal growth between liver and R. kidney. Small round-celled sarcoma. Bones: Extensive secondary deposits in vault and bone of skull, also in sternum. Other deposits: Liver invaded. R. kidney surrounded and involved. Blood examination: Red cells 2,050,000. Hb. 50 %. White cells 10,000. Polymorphs 41 %.

Case 29 (P. M. Records, vol. xxiii, no. 50). M.  $3\frac{1}{2}$  years. Duration: 2 months. Clinical course: Commenced with abdominal pain and swelling. Large firm mass filling up whole of right and middle divisions of abdomen. Systolic murmur over praecordium. Mass increased in size. Oedema of feet. No pigmentation. Urine normal. Primary growth: Large, soft, retroperitoneal tumour, closely applied to under surface of liver, but not attached to it. R. suprarenal not seen. 'Consisted of cells with small round and oval nuclei.' Liver: Few small nodules over 'bare area' of liver, also just under capsule in front. Lungs: Small circular ivory-coloured nodules at apex of R. upper lobe and apex of L. lower lobe. Few smaller nodules in R. lower lobe, in relation to bronchi. Kidney: L. unaffected. R. could not be found. Glandular and other deposits: Glands and nodules of growth on upper surface of R. diaphragm. Enlarged glands at junction of R. subclavian and internal jugular veins.

Case 30 (P. M. Records, vol. xxii, no. 296). F. 6 years. Duration: 13 weeks. Clinical course: Brought to hospital for lump in abdomen. On admission—pale and emaciated. Firm, hard tumour in abdomen, in middle and left divisions. Operation. Death. Primary growth: Large mass growing from medulla of R. suprarenal—part of unaffected cortex adherent. 'Cells with round and oval nuclei and small amount of protoplasm.' Liver: Several small secondary nodules on surface. Kidney: Both showed dilatations of pelvis, due to pressure on ureters. L. pelvis contained blood clot. Glandular and other deposits: Some retroperitoneal glands infiltrated. Growth spread forward between muscular and peritoneal layers of anterior abdominal wall.

Case 31 (P. M. Records, vol. xvii, no. 94). M.  $2\frac{1}{4}$  years. Duration: 3 weeks. Clinical course: Became pale and irritable, and then tumour noticed on R. side of abdomen. On admission, large mass felt in R. half of abdomen—kidney shaped. Small subcutaneous lump on R. 8th rib in posterior axillary line. Primary growth: Growth reached from under surface of liver to pelvis. R. suprarenal could not be found. 'Round-celled sarcoma.' Liver: Infiltrated. Growth adherent to lower surface. Lungs: Tumour had grown up behind liver and infiltrated diaphragm. Masses of growth on R. pleural surface of diaphragm. Kidney: R. kidney was small and lying in mass. Growth apparently beginning to infiltrate outer aspect of posterior wall.

Case 32 (P. M. Records, vol. xvi, no. 48). F.  $1\frac{1}{2}$  years. Duration:  $1\frac{1}{2}$  years. Clinical course: Brought up for abdominal swelling. On admission—large smooth tumour in R. side of abdomen. Urine contained pus, blood, and albumin. Operation—tumour partially removed. Primary growth: Large soft retroperitoneal tumour. R. suprarenal not seen. 'Sarcoma.' Liver: Few small growths, chiefly in R. lobe. Lungs: Lungs largely occupied by patches of new growth, especially at apices of both lower lobes and in R. upper lobe. Turbid fluid in both pleurae. Kidney: R. removed at operation. L. unaffected, but surrounded by tumour. Glandular and other deposits: Tracheal and bronchial glands slightly involved, and one large one behind L. sterno-clavicular joint. Retroperitoneal glands involved in tumour.

Case 33 (P. M. Records, vol. viii, no. 136). F.  $4\frac{1}{2}$  years. Duration: About 4 weeks. Clinical course: Fell against edge of table and complained of great pain, and later abdominal swelling was noticed and has increased. On admission—smooth, globular swelling in R. hypochondriac, lumbar, and iliac regions. Laparotomy. Death. Primary growth: Large mass reaching from under surface of liver to R. iliac fossa. R. suprarenal could be distinguished lying in tumour. 'Sarcoma.' Kidney: R. kidney much enlarged, with growth passing in at hilum. Kidney could be shelled off it. Glandular and other deposits: Under surface of diaphragm and head of pancreas involved.

Case 34 (P. M. Records, vol. vi, no. 202). F.  $2\frac{1}{2}$  years. Duration: 13 months. Clinical course: Has had swelling of abdomen and occasional pain. On admission—large tumour in R. side of abdomen. Urine normal. Later, R. leg and foot became swollen, and cervical glands enlarged. Primary growth: Growth of R. suprarenal, mass extending from diaphragm to R. iliac fossa. 'Encephaloid cancer.' Lungs: Small nodule in L. lower lobe. Two in R. middle lobe. Centre of R. lower lobe solidified and soft in parts. Kidney: Growth had passed in through hilum and normal renal tissue had become spread over it. Glandular and other deposits: Small nodule of new growth between uterus and bladder.

Case 35 (P. M. Records, vol. iv, no. 228). M. 4 years. Duration: 9 months. Clinical

curso: Swelling of abdomen and wasting. On admission—large tumour at site of R. kidney, and nodules felt below liver and in L. iliac fossa. Urine normal. Later, became jaundiced. Dullness over base of R. lung. **Primary growth:** R. suprarenal capsule affected, forming mass half the size of the kidney, but distinct from it. **Livor:** Common bile duct is embedded in mass, but patent. Tumour has grown into portal canals in bands, and forms masses around canals. **Kidney:** Mass has grown into R. kidney, and the renal pelvis is spread out over it. **Glandular and other deposits:** Mass of growth passing in between folds of mesentery.

Case 36 (P. M. Records, vol. iv, no. 202). M. 4 years. **Duration:** 7 months. **Clinical course:** Brought up for wasting, swelling of abdomen, and pain in L. side. No vomiting. Large mass in abdomen, more marked on L. side. Urine contains slight trace of albumin. **Primary growth:** Large mass contiguous to R. kidney and under surface of liver. **Liver:** Some small round nodules beneath capsule on upper surface. **Lungs:** Both pleurae partially adherent. Enlarged glands in lung, some pale caseous, some pulpy red and grumous. **Kidney:** Pelvis of L. kidney spread out on mass growing in at hilus. **Glandular and other deposits:** Retroperitoneal, bronchial, and mesenteric glands involved.

Case 37 (P. M. Records, vol. iv, no. 182). M.  $2\frac{3}{4}$  years. **Duration:** ? weeks. **Clinical course:** Began by vomiting a yellow fluid. A week later became jaundiced and motions white. Pain and swelling of abdomen. On admission—large tumour reaching from pelvis to umbilicus and into R. iliac fossa. Glands in both groins enlarged. Jaundice remained till death. **Primary growth:** Large retroperitoneal mass, extending round to anterior abdominal wall. Extends also between kidney and liver, and from here to under surface of diaphragm, which is completely invaded and about 1 in. thick. 'Lymphosarcoma.' **Liver:** Small secondary growths. Structures at portal fissure embedded in mass. **Kidney:** Small secondary growths in both, largest about size of 'hazel nut'. Both kidneys posterior to, and readily separated from, large growth. **Glandular and other deposits:** Small mass adherent to under surface of sternum in front of heart and R. lung.

Case 38 (P. M. Records, vol. iv, no. 58). M.  $2\frac{1}{2}$  years. **Duration:** 6 weeks. **Clinical course:** Pain in abdomen and diarrhoea. On admission—subcutaneous tumour in R. interscapular region over 8th and 9th ribs, smooth, firm, and non-fluctuating. Apical systolic murmur. Dullness on percussion over R. base of lung, bronchial breathing, and râles. Urine contained slight trace of albumin. Later, liver became much enlarged, and there was a large tumour in R. hypochondrium. **Primary growth:** Large retroperitoneal mass, situated to R. of and below liver, mostly chocolate colour, but part is yellowish and looks like substance of suprarenal. Mass spread across front of spine, and sends up a prolongation through diaphragm. 'Sarcoma.' **Livor:** About six small subcapsular growths, and one larger mass in substance above gall-bladder. **Lungs:** Large fleshy mass of new growth in R. pleural cavity, attaching lung to diaphragm, but can be separated. It projects backwards between ribs, giving subcutaneous nodules. Crosses vertebral column behind pleura to L. side. Some small pale-greyish nodules under the visceral pleura of both lungs. **Kidney:** R. kidney compressed and atrophied by growth. Contains a small pyramidal nodule, haemorrhagic, with base to surface. **Glandular and other deposits:** Some enlarged glands in pelvis.

Case 39 (P. M. Records, vol. iii, no. 120). F. 2 years. **Duration:** 3 weeks. **Clinical course:** Abdominal swelling and pain, and latterly swelling of legs. On admission—quantity of fluid in abdominal cavity, which was drawn off, and then a nodular swelling continuous with liver could be defined. **Primary growth:** Tumour in R. side of abdomen just below liver, and had prolongations forward under parietal peritoneum, also into mesentery. Adherent to R. side of diaphragm. 'Medullary cancer.' **Liver:** On posterior border and on under surface were whitish patches, and these extended a short distance into liver substance. Portal vein was compressed. **Glandular and other deposits:** Thoracic and bronchial glands somewhat enlarged and contained soft creamy matter.

Case 40 (P. M. Records, vol. ii, no. 99). M.  $2\frac{1}{2}$  years. **Duration:** 4 months. **Clinical course:** Began with abdominal pain, then swelling, and later lump was seen in R. lumbar region. No jaundice. No vomiting. On admission—hard tumour in R. loin, consisting of superficial mass with deeper nodules. **Primary growth:** Large mass between R. kidney and liver in situation of R. suprarenal. 'White encephaloid cancer.' **Liver:** Numerous small cancerous deposits. **Lungs:** Old adhesions on under surface of R. lower lobe. **Kidney:** Large mass

filled up pelvis of R. kidney. Kidney substance was stretched over it and could be detached. Glandular and other deposits: In posterior mediastinum was a mass of cancer, the size of a small pea.

Case 41 (From Museum Royal College of Surgeons). M. 5 years. Clinical course: Admitted to Fever Hospital with severe stomatitis and necrosis of jaw. Urine normal. No tumour felt on palpation of abdomen. Primary growth: Large growth in R. adrenal which invaded neighbouring portion of diaphragm. Liver: Many secondary deposits. Kidney: R. kidney separated by fibrous capsule from growth. Glandular and other deposits: Lobules of growth surrounding vena cava. Secondary deposit in mesenteric glands.

Case 42 (Lazarus). Sex? 4 years. Duration: 7 weeks. Clinical course: Swelling R. side of abdomen. No glandular enlargement. Urine normal. Later, oedema of feet and abdomen. Primary growth: Very large round tumour in position of R. suprarenal, with narrow strips of kidney at lower end. 'Round-celled sarcoma.' Kidney: R. kidney firmly attached and could not be separated.

Case 43 (Pitt). M. 10 months. Duration: About 12 weeks. Clinical course: Vomiting and diarrhoea for six weeks. Large tumour in abdomen, which steadily increased in size. Became drowsy and jaundiced. Primary growth: R. suprarenal had mass of new growth, size of egg. 'Vascular small round-celled sarcoma.' Liver: Large mass is greatly enlarged R. lobe of liver, with numerous secondary nodules scattered about. Glandular and other deposits: Gland in neighbourhood of suprarenal involved, with extension to head of pancreas.

Case 44 (Richards, Case XLIX). F. 8 months. Clinical course: Admitted for cough of one month's duration. Primary growth: R. adrenal contained a white growth, with haemorrhages into it, the size of a large pea. 'Round-celled sarcoma.' Lungs: Pleurisy and broncho-pneumonia on R. side.

Case 45 (Richards, Case XVIII). F. 2½ years. Duration: 4 weeks. Clinical course: Five weeks ago fell down stairs. One week later swelling noticed in R. side of abdomen, which has since increased. Large tumour in R. loin. Legs slightly oedematous. Primary growth: A large mass had originated in R. adrenal and destroyed it. 'Small round-celled sarcoma.' Liver: Tumour attached to liver, but not invading it. Lungs: R. lower lobe compressed. Kidney: Normal kidney tissue forming a capsule to large mass of new growth.

Case 46 (Eberth). F. 1½ years. Clinical course: Mass felt in abdomen. Ascites, diarrhoea. Primary growth: Growth in R. suprarenal. 'Myosarcoma.' Kidney: Growth in L. kidney. Glandular and other deposits: Metastases in peritoneum and diaphragm.

Case 47 (Gade). F. 6 years. Clinical course: Supposed to have psoas abscess or spondylitis. Primary growth: R. adrenal size of child's head. 'Round-celled sarcoma.' Liver: Metastases in liver. Lungs: Metastases in R. lung.

Case 48 (Earle and Weaver). M. 3 years. Duration: About 4 months. Clinical course: Jaundice, emaciation; rapid increase in size of liver, with improvement followed by relapse. Primary growth: Mass of altered suprarenal continuous with R. suprarenal, surrounding ducts in portal fissure. Prof. Welch says: 'Not certainly sarcoma,' but he is inclined to regard it as such. Liver: Surface olive green. No masses. Gall-bladder distended.

Case 49 (Pepper). F. 6½ weeks. Duration: ? 6½ weeks. Clinical course: Abdomen enlarged since four weeks old. Large abdominal mass. Liver 1 in. below umbilicus and large mass in R. iliac fossa and R. lumbar region posteriorly. Dullness all over this area. Child somewhat wasted. Primary growth: R. suprarenal enlarged, firm, haemorrhagic. On section yellowish-white with scattered areas of haemorrhage. Remnant of gland left at periphery. 'Lymphosarcoma.' Liver: Weight, 2 lb. 8 oz. Uniformly enlarged with no irregularities. Capsule smooth, mottled with reddish and yellowish areas. On section appearance similar to suprarenal.

Case 50 (Gade). M. 4 years. Clinical course: Pain, emaciation, and abdominal tumour. Primary growth: Both suprarenals involved in one mass size of child's head. 'Round-celled sarcoma.' Liver: Metastases in liver.

Case 51 (Orr). F. 15 weeks. Duration: 2 months. Clinical course: Large abdominal

mass. No pigmentation. Child gradually became weaker. Primary growth: Both supra-renals affected, R. much more than L. 'Round-celled sarcoma, but extending like carcinoma.' Liver: Numerous yellowish-white growths.

## REFERENCES.

1. Aisenstein, *Beiträge*, 3. 'Kasuistik der Nebennierentumoren im Kindesalter.' (Cited by Tileston and Wolbach.)
2. Brück, *Jahrb. f. Kinderheilk.*, 1905, lxii. 84.
3. Bulloch and Sequeira, *Trans. Path. Soc.*, Lond., 1905, lvi. 189.
4. Caillé, *Arch. Pédiat.*, New York, xii. 1895. (Cited by Pepper.)
5. Chaffey, *Trans. Path. Soc.*, Lond., 1885, xxxvi. 415.
6. Cohn, *Berl. klin. Woch.*, 1894, xxxi. 266.
7. Dalton, *Trans. Path. Soc.*, Lond., 1885, xxxvi. 247.
8. Earle and Weaver, *Journ. Amer. Med. Assoc.*, Chicago, 1894, xxiii. 980.
9. Eberth, *Virchow's Archiv*, Berlin, 1872, lv. 518. (Cited by Pepper.)
10. Gade, *Forhand. Norske Med. Selskab.*, Christiania, 1886. (Cited by Pepper.)
11. Guthrie and Emery, *Trans. Clin. Soc.*, Lond., 1907, xl. 175.
12. Handley, *Lancet*, Lond., 1905, i. 1048.
13. Hektoen, *Textbook of Pathology*, Hektoen and Reisman, ii. 662.
14. Hutchison, *Quart. Journ. Med.*, Oxford, 1907-8, i. 33.
15. Lazarus, *Berl. klin. Woch.*, 1894, xxxi. 498.
16. MacCarty, *Berl. klin. Woch.*, 1905, xlii. 115, Festnummer f. Ewald. (Cited by Tileston and Wolbach.)
17. Mann, *Proc. Royal Soc. Med.*, Lond., 1909, Sect. 'Disease in Children', ii. 1. 160.
18. Ogden and Matthews, *Brit. Journ. of Children's Diseases*, iii. 394. (Cited by Hutchison.)
19. Orr, *Edin. Med. Journ.*, 1900, N. S., viii. 221.
20. Parker, *Trans. Path. Soc.*, Lond., 1880, xxxi. 290.
21. Pepper, *Amer. Journ. Med. Sci.*, 1901, cxxi. 287.
22. Pitt, *Trans. Path. Soc.*, Lond., 1898, xlix. 143.
23. v. Recklinghausen, 'Die fibröse und deformirende Ostitis der Osteomalacie und die osteoplastische Carcinose in ihren gegenseitigen Beziehungen,' *Festschr. zu Virchow zum 71. Geburtstage*, Berlin, 1891.
24. Richards, *Guy's Hosp. Rep.*, Lond., 1905, lix. 217.
25. Rolleston, *Allbutt and Rolleston's System of Medicine*, Sect. 'Ductless Glands', Lond., 1908, iv. 1. 429.
26. Targett, 'Multiple Sarcoma of Skull, Ribs, and Glands,' *Trans. Path. Soc.*, Lond., 1888, xxxix. 306.
27. Tileston and Wolbach, *Amer. Journ. Med. Sci.*, 1908, cxxxv. 871.

## DESCRIPTION OF FIGURES.

PLATE 19, FIG. 1. Case 1. Photograph of inner aspect of calvarium, showing secondary deposits. (Dura has been removed.) Photograph by G. B. Wainwright.

FIG. 2. Case 2. Photograph taken Sept. 3, showing ulceration of R. cornea, also proptosis of L. eye.

FIG. 3. Case 2. Photograph taken August 24, showing exophthalmos of R. eye and swelling over R. external angular process.

FIG. 4. Case 3. Photograph showing exophthalmos of both eyes, more marked in left.

FIG. 5. Case 3. Photograph of calvarium (outer aspect), showing numerous secondary growths.

PLATE 20. Case 3. Painting of primary growth, showing tumour in section, kidney at lower pole, mass of enlarged glands at its hilum.

PLATE 21. Case 29. Painting showing liver flattened out by growth, L. kidney unaffected. Secondary nodules on upper surface of diaphragm and in lungs.



FIG. 1



FIG. 2



FIG. 3



FIG. 4









FIG. 6.





FIG. 7.



# NOTES UPON ALTERNATION OF THE HEART

By THOMAS LEWIS<sup>1</sup>

(From University College Medical School)

With Plate 22

AMONGST the several affections of its mechanism to which the human heart is subject, none perhaps is less understood than alternation of the strength of its contractions. A great many observations have been made in regard to it, but the explanation of its production is still wrapped in obscurity.

During the course of a systematic investigation of cardiac irregularities, clinical and experimental, I have met with heart alternation in slight and marked degree on many occasions. From a number of observations a few, hitherto undescribed, have been selected for publication.

Heart alternation occurs under two circumstances. It is seen when the cardiac muscle is not of necessity altered structurally, as an accompaniment of great acceleration of the rate of rhythm. It is also found when the pulse is of normal rate, and under such circumstances the muscle is either markedly degenerate or the heart shows evidence of embarrassment as a result of poisoning or some other factor.

The observations now published are drawn from the first group.

## *Divergent Alternation.*

In studying the effect of ligation of the coronary arteries, it was found that an obstruction of one or the other is usually followed by the appearance of rapid and new rhythms arising in the ventricle; and a detailed account of such rhythms will be found in another place (3). Suffice it to say that the ventricular rhythm dominates that of all the cardiac chamber; and that if the heart rate is greatly increased, alternation frequently appears. Examples of the curves obtained under these conditions are shown in Figs. 1 and 2. The four tracings of Figs. 1 and 2 were each obtained in similar manner. The uppermost curve in each is a ventricular myocardiograph, taken with a modification of Roy and Adami's instrument; the points of attachment were transversely across the centre of the heart. The second curve in each is a similar record from the right auricle. The third curve is a carotid pressure tracing, taken with a Hürthle manometer.

In a recent paper Hering has published simultaneous apex and radial curves from the dog and from a clinical case, which appear to demonstrate that, when alternation in excursion in both is manifested, the larger excursion in one

<sup>1</sup> Working under the tenure of a Beit Memorial Research Fellowship.

may be found to correspond to the smaller excursion in the other. The fact that the large apical curve may correspond to the smaller radial beat seems such a remarkable phenomenon, that, regarded as an expression of the relationship of the strength of ventricular contraction and the amplitude of the corresponding arterial curve, it can hardly meet with acceptance in the absence of confirmatory and more direct evidence. This evidence is provided by the three accompanying curves (Fig. 1). The curves represent a paroxysm of regular tachycardia in which the auricle is responding to the ventricle. Attention is drawn to the fact that in these curves the systoles of the ventricle (above) and of the auricle (below) are represented by downstrokes. They illustrate the changed relationship which may be found in ventricular, auricular, and carotid curves within short spaces of time. A few seconds intervene between each strip. In the first curve the large ventricular beat corresponds to the large auricular beat and to the large carotid upstroke. In the second curve the large ventricular beat corresponds to the large auricular and to the small carotid beat. In the third curve the large ventricular beat corresponds to the small auricular beat and to the large carotid beat.

It is shown, therefore, that the excursion of the arterial curve, when alternation is present, is not necessarily associated with parallel alternation in the amplitude of the ventricular muscle excursion, and that in one and other the alternation may be divergent. The simultaneous alternation in the auricle is of special interest. It is clearly shown to be independent of the ventricular alternation by a comparison of the first two with the last curve, for in the first two curves the auricular and ventricular alternations run with parallelism, while in the last they are divergent. Now if the exact relationship of the auricular and ventricular systoles be compared in any one of these curves it will be found that the auricular systole commences a trifle before the beginning of the diastole of the ventricular cycle to which it belongs (and to the contraction of which it is a response), and that it extends well into the said diastole. In brief, the auricular systoles are efficient in that they aid the filling of the ventricle. We have an immediate and I believe helpful clue to the appearance of divergent alternation in ventricle and carotid in the middle curve, for in this tracing, as opposed to the first, the auricular alternation is marked in its degree. The strong carotid pulsation is the result of the weak ventricular contraction, but the efficiency of the latter is reinforced by the preceding strong auricular contraction; similarly the small carotid pulsation is the outcome of the strong ventricular contraction, but the efficiency of the latter is embarrassed by the relatively small influx of blood as a result of the preceding weak auricular contraction. A comparison of the middle and right-hand curves (Fig. 1) will show that the ventricular excursion is of equal extent in each. The auricular and carotid alternations taken together are also divergent in each; but in the one instance the divergent auricular alternation increases the carotid alternation (right-hand curve), while in the other it diminishes it (middle curve).

The explanation offered of the curious anomaly presented by the middle

figure, namely, divergence of ventricular and carotid alternation, is strongly supported by further observation upon the same animal (the whole series of curves was obtained within a space of three minutes, and they are given in the order of their occurrence). At the commencement and ending of this figure (Fig. 2), strips of alternation are shown in which the occurrences are similar to those seen in Fig. 1 (right-hand curve). Over the central portion of the strip the vagus was stimulated; the ventricle is beating in response to inherent impulse formation, and the sole effect of the vagus excitation, in this instance, is the temporary suspension of auricular activity. But at three points an auricular response to ventricle is recorded, and the effects of these three beats are strikingly shown in the carotid curve. The first escaped auricular beat (1) falls *during* a *weak* ventricular contraction (1), and its influence is felt by the succeeding strong carotid pulsation (1), which is markedly exaggerated. The next auricular contraction (2) is a response to a *strong* ventricular systole (2), with which it falls; as a consequence it causes a temporary abolition of alternation in the carotid, by increasing the amplitude of an expected weak carotid beat (marked 2). The third response shows similar time relationships to the first, and gives rise to similar carotid changes; but it may be noted that just as the third auricular beat is weaker than the first, so the third carotid beat is weaker than the first.

As a result of these observations, therefore, it seems clear that certain instances of divergent alternation in ventricle and carotid may be the result of simultaneous alternation in the auricle.<sup>2</sup> A curve has been published by Volhard which supports this view. He gives simultaneous curves from jugular, apex, and radial in a patient exhibiting alternation. In his figure (Fig. 1) the larger apical curve corresponds to the smaller radial beat, but alternation is also seen in the amplitude of the  $\alpha$  waves in the jugular, and in this instance the small radial beat is preceded by the small  $\alpha$  wave.

#### *The Electrocardiogram in Clinical Alternation.*

This note upon heart alternation may be concluded by a brief description of some electrocardiographic curves obtained from a patient, the subject of auricular tachycardia, whose case has been otherwise fully described in a previous communication (3). The facts in regard to the electric curves in alternation are already known as a result of experimentation (1 and 2), and their publication is chiefly demanded because it brings the clinical and experimental appearances more closely into line.

Each of the accompanying photographs portrays an electrocardiogram and radial curve from the same patient. All are from paroxysmal periods, and the abnormal (in this case inverted)  $P$  variation is seen superimposed upon  $T$ , the second ventricular variation. It notches it in a downward direction, occurring at the commencement of  $T$  in Fig. 3, I and III, and near the apex of  $T$  in

<sup>2</sup> It should be stated that the auricular myocardiogram was obtained from the right auricle, and that it is assumed that alternation was also present in the left.



Fig. 3, II. It will suffice if the chief points demonstrated by the curves are noted. The shape of each ventricular complex shows it to result from a contraction of supraventricular origin. The distinction between alternation and premature ventricular contractions arising late in the cycle is clearly defined. From beat to beat the curves are similar in their general conformation; they fail to support the view expressed by Hering that alternation may result from intraventricular heart-block, for under such circumstances a notable change in the general outline from beat to beat would be expected.

The alternate beats show only slight quantitative changes in the several peaks. The short *R* is usually accompanied by a slightly exaggerated *T* (Fig. 3, I), though it may be accompanied by a diminished *T* (Fig. 3, II), or by a *T* in which no change is detected.

The relationship to alternation in the arterial curve is equally variable and equally obscure. In the beginning of Fig. 3, I, alternation in *R* runs parallel with that of the pulse for the first four beats. That is to say, the tall *R* corresponds to the slightly taller radial beat. In the last beats of the same photograph the trace of alternation in the pulse vanishes, while the alternation of *R* increases somewhat. Alternation of the pulse to extinction is shown in the next figure, and the complex composed of a high *R* and a high *T* is associated with absent radial pulsation. In the last figure alternation is well defined in the radial curve, while it is not discoverable in the electrocardiogram.

The explanation of these phenomena is unknown, and a discussion of them is impossible at the present time.

### Conclusions.

1. Divergent alternation of ventricle and carotid, a condition in which the large ventricular contraction corresponds to the small carotid upstroke, is encountered experimentally. The divergence is due in some instances to simultaneous alternation of the auricle.

2. The electrocardiographic curves obtained in clinical heart alternation are similar to those obtained experimentally; there is a divergence between the heights of *R* and *T* and the amplitude of the radial upstrokes. These facts demonstrate the identity of the clinical and experimental conditions.

### REFERENCES.

1. Hering, *Münch. med. Wochenschr.*, 1908, lv. 2. 1417; *Zeitschr. f. exper. Pathol. u. Therap.*, Berlin, 1909, vii. 363.
2. Kahn and Starkenstein, *Arch. f. d. ges. Physiol.*, Bonn, 1910, cxxxi. 579.
3. Lewis, *Heart*, Lond., 1909-10, i. 98 and 262.
4. Volhard, *Münch. med. Wochenschr.*, 1905, lii. 1. 590.

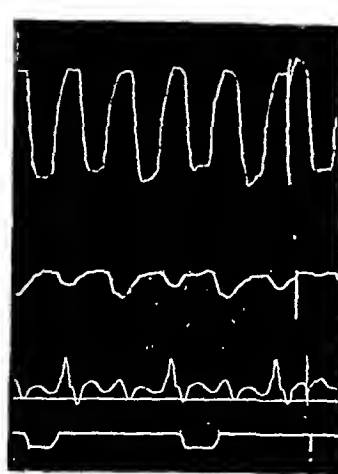
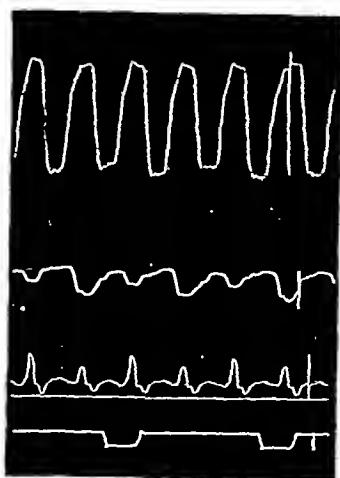
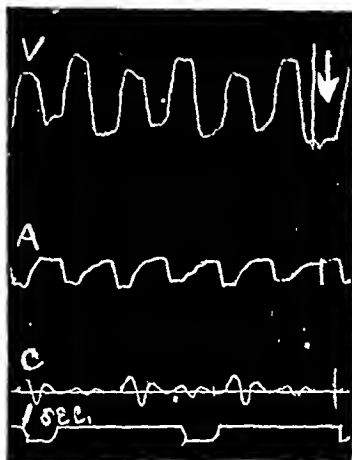


FIG. 1

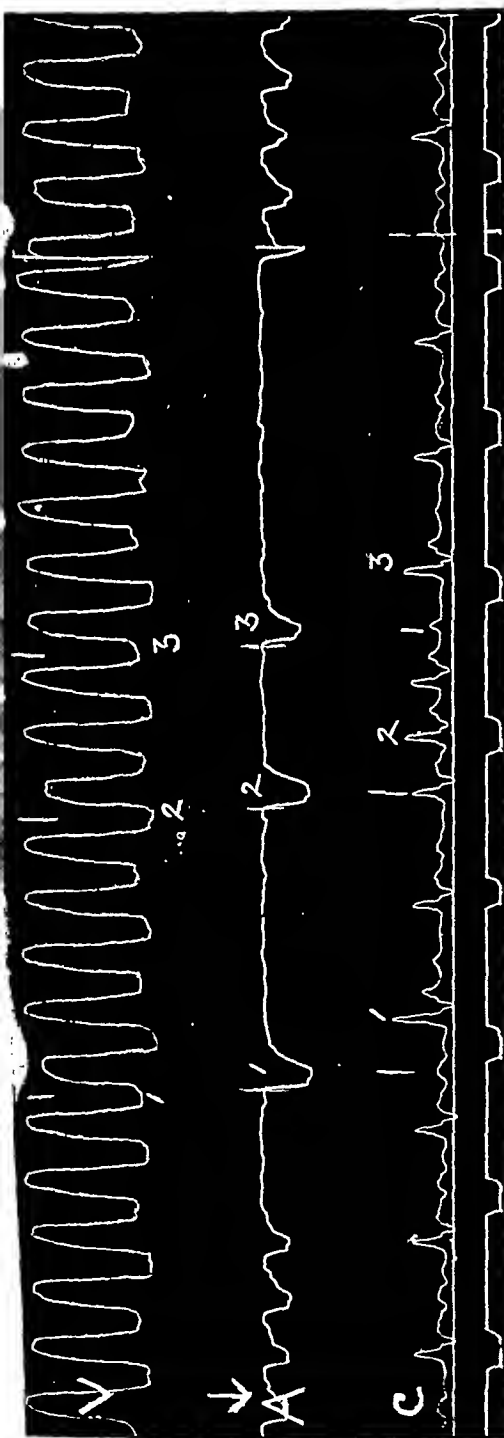


FIG. 2



FIG. 3



# THE INFLUENCE OF CERTAIN FACTORS UPON ASPHYXIAL HEART-BLOCK

BY THOMAS LEWIS<sup>1</sup> AND B. S. OPPENHEIMER

With Plates 23-25

THE experimental study of auriculo-ventricular heart-block in the intact animal is not without difficulty, for at the point at which the bundle may be divided with convenience, it lies in the septum separating the ventricles or the septum between the right auricle and left ventricle. To produce a lesion of the bundle, by section and with certainty, necessitates transfixation of this septum. As a consequence a communication between left ventricle and either right auricle or right ventricle is a customary result. The method of incision with the heart beating *in situ* is therefore impracticable as a routine procedure.

The difficulty may be avoided by the employment of sutures, so arranged as to include the bundle, and this method has been adopted by the Berne school. But it is apparent that the placing of such sutures is not accomplished with facility; a single suture is frequently insufficient, and a large number of the experiments are totally abortive. When experiments are directed not merely towards the production of heart-block, but towards the further investigation of heart-block once produced, it becomes essential that more certain means of inducing it should be obtained. This end has been accomplished by Erlanger and his co-workers by means of a special clamp, devised to penetrate the intra-ventricular septum, and to include between its jaws the upper portion of the septum, the bundle and the tissues lying directly at the base of the ascending aorta.

In a paper which appeared in a recent number of *Heart*, one of us, working with Mathison (3), described a series of experiments upon the asphyxial heart, originally observed by Sherrington (5). It was clear that we were in possession of a sure means of producing heart-block in its several grades, and that as a consequence we could conveniently utilize asphyxia as a method of producing heart-block and could study the heart-block so produced.

The present observations were undertaken with the object of determining the influence of acceleration of the auricular rate upon impaired conduction; of ascertaining the effect of premature ventricular contractions, single or successive, upon the same transmission from auricle to ventricle; of studying

<sup>1</sup> Working under the tenure of a Beit Memorial Research Fellowship.

the influence of slight grades of conduction damage upon the retrogression of impulses from ventricle to auricle; and of determining the influence of vagal stimulation upon partial heart-block. Some of the observations have already been undertaken by Erlanger (2) and Erlanger and Hirschfelder (1), who produced heart-block by compression of the bundle with their specially devised clamp. We considered it essential to confirm in asphyxial heart-block the observations made by these writers on heart-block resulting from mechanical compression, and if possible to extend their observations.

*Method.* Cats have been employed exclusively. They have been anaesthetized with a preliminary injection of urethane, in an approximate dosage of one and a half grams per kilogram of body weight, and by the subsequent administration of a sufficiency of chloroform. In the earlier experiments we employed the intact chloroformed and curarized animal; in the later observations we decapitated the cats. In the earlier experiments we sometimes cut the vagi and sometimes preserved them. We have found no essential difference in our results according to the adoption of one or other of these several procedures.

Premature beats were induced by means of induction shocks, single or successive and regular, and applied to auricle or ventricle. The fish-hook electrodes attached to auricle and ventricle were introduced through small windows in the chest-wall, which were subsequently closed, so that the heart might lie within the thorax in as natural a position as possible. No air was permitted to remain in the pleural spaces.

Asphyxia was provoked by the suspension of artificial respiration. Preliminary observations were made to ascertain the times of the onset of the several grades of heart-block in the individual animals. In this manner the auricle and ventricle could be stimulated at will, during a phase of any degree of heart-block manifested by the animal under investigation.

The heart-block which occurs in asphyxia progresses from a slight to a higher grade, and as a general rule, when a particular grade of heart-block is established, there is no break-back to a lower grade, so long as the asphyxia persists. A special factor, as for example auricular tachycardia, may temporarily increase the degree of such a slowly progressive heart-block. When one is studying the effect of various factors upon the original degree of asphyxial heart-block, a change from a lesser to a greater grade may be pronounced as due to the interfering factor, and not as constituting a step in the regular succession of heart-block changes produced by the asphyxia itself when, at the cessation of the interference, that grade of heart-block is re-established which existed prior to such interference. We take as our criterion of the production of an increased grade of heart-block by an interfering factor, the constant appearance of the increase of grade at a time when the interference occurs; and reject all observations in which the pre-existing degree of heart-block fails to reappear immediately upon, or soon after, the cessation of stimulation. For under the last-mentioned circumstances it would be impossible to declare that the increased grade of heart-block is due to stimulation, and not to the asphyxia *per se*.

Asphyxial heart-block is associated with considerable distension of the auricular portion of the heart, and although heart-block be observed by inspection of the chambers, myocardiograms are difficult to obtain on account of the feeble movement present in the auricle at such times. We have consequently employed the string galvanometer, leading from the right fore-leg and left hind-leg, as the most convenient and certain method of obtaining records.

### *The Effects of Auricular Tachycardia.*

In control observations, in which the transmission interval is of normal length (for cats, 0.08 to 0.12 sec.), auricular tachycardia, resulting from a succession of regular induction shocks thrown in at a more rapid rate than the natural heart rhythm, usually produces little or no effect upon the conduction time. On occasions, however, and with very rapid tachycardia, we have noticed a reduction of the P-R interval.

The effect of an auricular tachycardia upon conduction during the earliest phase of asphyxial heart-block, namely, when the P-R interval is prolonged, varies considerably in different animals; but it is consistent in this respect, that it invariably induces an enhanced degree of block. Thus the acceleration of auricular rate may cause a further and gradual increase of this P-R interval, and the increase may be followed to a point at which single blocked beats occur, or at which 2:1 heart-block is established (Figs. 1 and 2). On other occasions, an abrupt rise in the degree of heart-block may be seen. A prolonged P-R interval may give place immediately to a 2:1 and eventually to a 3:1 rhythm; on rarer occasions, but not uncommonly, complete dissociation supervenes (Fig. 2). As a rule a short strip of curve intervenes between the prolonged P-R interval and the complete heart-block stage, and during such a period a high grade of partial block is present, e.g. 2:1 or 3:1 heart-block, or a succession of ventricular beats occurring at irregular intervals in response to auricular impulses (Fig. 3). Thus to illustrate the last phenomenon, a prolonged P-R phase may be succeeded at the supervention of auricular tachycardia by a 2:1 then 6:1, 5:1, 4:1, 6:1, 3:1 cycle. Such periods constitute the nearest approach which we have encountered during the present experiments to stoppage of the ventricles as described by Erlanger and Hirschfelder. The longest intervals of 'stoppage' were of about 2 seconds' duration.

When 2:1 heart-block has been established as a result of asphyxia, a tachycardia arising in the auricle varies in the effect according to the rate of such tachycardia and according to the duration of the 2:1 phase. Thus in the early stages of 2:1 asphyxial heart-block an increase of auricular rate may actually lead to an increase of ventricular rate with a maintenance of 2:1 rhythm (Fig. 5). This fact does not necessarily signify the absence of an increased obstruction to the passage of auricular impulses at such times. The phenomenon is not observed during the later stages of a 2:1 rhythm, for at such times the

2:1 phase gives place to higher grades of heart-block. Variation in the results in the earlier and later stages of 2:1 heart-block meets with an obvious explanation. During the whole of the asphyxial experiment, the grade of the heart-block is increasing, although the increase is only conspicuous at the beginning and at the termination of the 2:1 phase. During the early stages of the 2:1 phase the junctional tissues are capable of transmitting impulses at a faster rate than they are actually called upon to do, whereas towards the end of the 2:1 stage they are transmitting impulses at the maximal rate.

A 2:1 heart-block, when fully established, may be converted by auricular tachycardia into 3:1, 4:1, or complete heart-block; in the last instance, with or without the interpolation of cycles of partial heart-block of higher grades (Fig. 4). At the cessation of stimulation a partial over-recovery is observed, i.e. a temporary return to a lower grade of heart-block than that which prevailed before the stimulation. For example, we have observed a 2:1 block converted by an auricular tachycardia to successive cycles of 6:1, 3:1, 4:1 block; while on cessation of the auricular tachycardia one cycle of 2:1 block occurred and was followed by three 1:1 cycles, accompanied by a prolonged P-R interval. At a later period there was a return to a persistent 2:1 rhythm.

A phenomenon which we have not uncommonly encountered in decapitated cats, and for which we can offer no explanation, may be observed at the termination of auricular tachycardia induced during a stage of asphyxial heart-block. The whole heart may stand still for prolonged periods. There is eventual recovery. The periods of stand-still of the heart have extended through varying intervals up to three seconds. They may occur during the stages of prolonged P-R interval, or 2:1 heart-block (Fig. 3).

#### *The Effects of Induced Ventricular Beats upon Auriculo-Ventricular and Ventriculo-Auricular Conduction.*

The effect of single excitations, applied to the ventricle, is variable from animal to animal, but is most pronounced where a considerable grade of heart-block is present; for example, a single premature beat, falling just before an expected response of ventricle to auricle during a 2:1 heart-block stage, hinders this response and the response to the succeeding auricular impulse. That is to say, the single premature beat replaces the usual ventricular beat, which is a response to one of the alternate auricular impulses. Even though the premature ventricular contraction falls earlier in a 2:1 cycle, so that the succeeding auricular impulse falls clear of the refractory period, the same events occur; there is an absence of response, both to this and the succeeding auricular impulse (cp. Erlanger's experiments upon compression heart-block).

A further exaggeration of this phenomenon is shown in Fig. 6. A single premature ventricular beat occurring during a 2:1 heart-block phase produces an absence of response to three auricular contractions, and the first ventricular beat is apparently ideo-ventricular in origin.

The effect of successive ventricular beats is often more pronounced. Induced ventricular tachycardia during the prolonged P-R stage may result in a temporary further prolongation of the P-R interval or in a temporary 2:1 heart-block at the cessation of stimulation. Again, the effect of a similar ventricular tachycardia during a period of 2:1 heart-block is manifested by the production of short periods of increased block at the termination of such tachycardia. This increased block may be a 3:1 heart-block, a 4:1 heart-block, or on rare occasions complete heart-block, lasting for a few cycles; each is followed by the reappearance of the original 2:1 rhythm which preceded stimulation (Fig. 7, *A*, *B*, and *C*).

In all these experiments it is noticeable that the degree of enhanced heart-block is largely dependent upon the length of the induced ventricular tachycardia. With short periods there may be no increase of the block, with longer periods it is almost invariable, and usually the block reaches a high grade.

It is obvious that induced ventricular beats have a distinct influence on the conduction of impulses from auricle to ventricle, when this conduction is primarily impaired by asphyxia. In none of the control experiments has there been any influence of this nature, so long as the P-R was of normal duration.

The question arises as to how this increase of heart-block as a result of induced ventricular beats is produced. The increase is in no way attributable to the steady progression of the grade of heart-block occurring during the asphyxial experiments. The temporary enhancement of heart-block gives place to a return to the original degree present directly prior to stimulation, in the great majority of the experiments.

In considering this question the effect of induced ventricular tachycardia upon the retrogression of impulses to the auricle is of importance. Successive and induced ventricular beats, following each other regularly and at a rate more than sufficient to outpace the normal auricular impulse formation, retrogress in control experiments from the third to the twenty-seventh cycle (usually between the fifth and the twelfth cycle). On the other hand, a prolongation of the P-R interval from, say, 0.08 sec. to 0.14 sec. absolutely prevents the occurrence of retrograde contraction. The same applies of course to higher grades of heart-block, i.e. 2:1 heart-block, 3:1 block, &c. (Fig. 7).

In brief, ventricular tachycardias occurring during the stage of heart-block are never retrograde; yet these same tachycardias bring about a striking increase in the degree of heart-block originally present (Fig. 7). The increase of heart-block, therefore, cannot be rationally attributed to fatigue of the *A-V* bundle as a result of its possible contraction in response to the impulses of the induced ventricular beats, for we have evidence that the upper portions of the junctional tissues are not affected by these tachycardias. It seems probable that the increased grade of heart-block is the result of fatigue of the lowest levels of the junctional tissues, perhaps of the arborizations of the main branches of the bundle. The actual level of the fatigue cannot be fixed.



*The Effects of Vagus Stimulation upon partial Heart-Block.*

In their clamp experiments, Erlanger and Hirschfelder state that stimulation of the vagus during periods of partial heart-block is not accompanied by an increase in the grade of the block. At a later date Erlanger writes, 'Stimulation of the vagus nerve sometimes causes a block to develop at the auriculo-ventricular junction of the normal heart. But on the other hand, stimulation of this nerve during partial heart-block may remove, or diminish the intensity of, the block.'

We have investigated the effects of vagal stimulation upon the partial heart-block of asphyxia, and find that the effect is very definite. The essential difficulty experienced by Erlanger lay in the fact that with the stimulation of the inhibitory nerves, the resultant slowing of the auricle complicated the reading, and rendered it difficult to ascertain the actual degree of change which occurred in the facility with which the impulses were transmitted. In the present experiments this difficulty has been obviated by maintaining a constant auricular rate with interrupted induced shocks. It is necessary to use a relatively high strength of current, for, during the heart-block stage and more especially during the period of vagal stimulation, the excitability of the auricle is markedly depressed. The actual electrical shocks consequently often appear upon the curves (Fig. 9). Stimulation of the vagus during the period when the P-R interval is prolonged produces a high grade of partial heart-block (Fig. 8). The same applies to stimulation during 2:1 phases of heart-block. The effect is almost immediate (Fig. 9). The next anticipated response of the ventricle is missed, and as a rule there is no further response until several auricular cycles have passed, subsequent to the termination of the vagal stimulation. The recovery is rapid, and usually that grade of heart-block appears which was present before the excitation of the vagus. On some occasions an over-recovery has been noted.

*Summary.*

The results of this investigation may be briefly stated as follows:—An increase of auricular rate during the heart-block caused by asphyxia increases the grade of heart-block. The observation is parallel with that made by Erlanger and Hirschfelder in their clamp experiments.

Single premature ventricular beats and ventricular tachycardias likewise produce an increase in the grade of a preceding asphyxial heart-block, but we find the increase to be more pronounced than Erlanger has stated it to be in his clamp experiments. A single premature ventricular contraction occurring just antecedent to an expected ventricular response may lead to a failure of three or more ventricular responses to auricle. Tachycardias of ventricular origin are usually succeeded by marked grades of increased block.

The increase in the degree of heart-block following single ventricular beats or ventricular tachycardia is brought about independently of the retrogression of the ventricular impulses to the auricle.

The heart-block of asphyxia reacts to certain interfering factors, such as auricular and ventricular tachycardia, in a similar manner to the heart-block produced by compression of the auriculo-ventricular bundle.

The partial heart-block of asphyxia is enhanced by stimulation of the vagus.

# REFERENCES.

1. Erlanger and Hirschfelder, *Amer. Journ. Physiol.*, 1905-6, xv. 153.
2. Erlanger, *Amer. Journ. Physiol.*, 1906, xvi. 160.
3. Lewis and Mathison, *Heart*, Lond., 1910, ii. 47.
4. Roaf and Sherrington, *Quart. Journ. Exper. Physiol.*, Lond., 1910, iii. 209.
5. Sherrington, *Journ. Physiol.*, Camb., 1909, xxxviii. 381.

# DESCRIPTION OF FIGURES.

PLATE 23, FIG. 1. ( $\times \frac{9}{9.5}$  linear.) Cat XVI. Intact, chloroformed, and eurarized. Vagi cut.

An electrocardiographic curve, taken 1 min. 25 sec. after the onset of asphyxia, and at the end of a period of interrupted stimulation of the auricle. Before the onset of stimulation the P-R interval was of the same duration as that shown at the end of this figure; it was slightly prolonged. During the tachycardia it shows progressive increase, so that the auricular systole falls back further and further upon the preceding ventricular systole. In the terminal phases of stimulation, three responses are missed. At the actual cessation of stimulation, recovery is manifest. In this as in all the succeeding figures, the upper line represents the signal of induction shocks; the second line,  $\frac{1}{2}$  sec.; the third, the electrocardiograms.

FIG. 2. ( $\times \frac{9}{13.5}$  linear.) Cat XIX. Decapitated cat. 1 min. 45 sec. after the onset of asphyxia. A curve taken during the phase of prolongation of the P-R interval and showing the effect of interrupted induction shocks thrown into the auricular tissue. The prolonged P-R interval shows a further increase in the early phases of stimulation, and at the point marked in the curve passes into a 2:1 rhythm; at a further point marked in the curve dissociation appears. Complete recovery to a slightly prolonged P-R follows the cessation of stimulation.

FIG. 3. ( $\times \frac{9}{13.5}$  linear.) A curve taken from the same animal some 40 sec. later. The auricle was stimulated during the prolonged P-R stage. The induction shocks produced a high grade of partial heart-block, and at their cessation a long period of 2 sec. occurred, during which the whole heart stood still. Complete recovery is shown in the last three cycles of this tracing. Such stoppage of the whole heart is but an occasional event.

FIG. 4. ( $\times \frac{9}{13.5}$  linear.) Cat XVI. Intact, chloroformed, and eurarized. Vagi cut. A record taken 1 min. 55 sec. later than Fig. 1 and from the same animal. The stimulation, during 2:1 heart-block, preceded the record and is not shown; the effects are manifested up to a point where the second ventricular beat occurs. The first and probably the second ventricular beats are ideo-ventricular. The last three cycles belong to a 2:1 period. The first two ventricular beats are considered ideo-ventricular on account of the variation in the shape of the ventricular complexes.

PLATE 24, FIG. 5. Cat XVI. Intact, chloroformed, and eurarized. Vagi cut. 1 min. and 40 sec. after the onset of asphyxia. A curve taken during the earliest period of a phase of 2:1 heart-block, and showing the effect of a slight increase in the rate of the auricle, as a result of interrupted induction shocks applied to it. Where the 2:1 heart-block has been of but short duration, such slight increases of rate may not increase the apparent grade of heart-block, but may actually increase the ventricular rate, as in this instance. It does not necessarily follow that the grade of heart-block is decreased; there is every reason to believe that it may be increased at such times.

FIG. 6. ( $\times \frac{9}{10}$  linear.) Cat XIII. Intact, chloroformed, and curarized. Vagi not divided.

An electrocardiogram taken 1 min. 50 sec. after the beginning of asphyxiation, during the stage of 2:1 heart-block. The accompanying curve shows two cycles of the 2:1 heart-block, and at a point marked by an asterisk a premature beat is excited in the right ventricle by means of a single induction shock; the response to the excitation occurs at a point just preceding that at which the auricular contraction ( $P_2$ ), to which a response is expected, falls. As a result of this abnormal ventricular contraction, the expected response of the ventricle to the succeeding auricular contraction is missed, and two additional auricular contractions,  $P_3$  and  $P_4$ , take place without response. The first ventricular contraction is an escaped beat and it falls directly after  $P_5$ . There is no response to  $P_6$ , but there is to  $P_7$ ; 2:1 rhythm is resumed. The effect of the induced ventricular contraction upon conduction is marked; it is more marked than usual, for in most instances a response of the ventricle would occur to  $P_4$  or  $P_5$ .

FIG. 7. ( $\times \frac{9}{11}$  linear.) Cat XXI. Decapitated cat. An electrocardiogram taken during

a stage of 2:1 heart-block, and showing the effect of an induced ventricular tachycardia upon the transmission of impulses from auricle to ventricle. The first of the successive excitations falls in the refractory period of the ventricle; the second and third are effective and are shown in the first strip (7A). The ventricular tachycardia is continued from this point through twenty-three cycles; the nineteenth to twenty-third cycles are shown in the second strip (7B). It is to be observed that throughout the whole of this tachycardia stage the ventricular impulses are never retrogressive to the auricle. At the cessation of stimulation, two clear cycles of 4:1 rhythm are seen; three additional cycles of the same kind are omitted. The subsequent return to 2:1 heart-block is shown in the third strip (7C). The figure illustrates the increase of a pre-existing heart-block as a result of ventricular tachycardia, none of the contractions of which are transmitted to the auricle.

PLATE 25, FIG. 8. Cat XXV. Intact, chloroformed, and curarized. Vagi intact. A curve taken during the stage in which the P-R interval is prolonged. An additional record, that of vagal stimulation, is seen in the uppermost line in this figure, and in Fig. 9. The auricle is responding throughout to regular induction shocks; its rate is therefore constant. The vagus was stimulated at the point marked by the arrow, and from this point onwards the ventricle fails to respond.

FIG. 9. A similar curve from the same animal as Fig. 8, showing the effect of vagal stimulation during a phase of 2:1 heart-block. The vagal stimulation commenced at the point marked by the arrow, and from this point onwards isolated auricular beats,  $P_1$ ,  $P_2$ ,  $P_3$ , &c., continued. The vagal stimulation continued up to  $P_{15}$ . The first response of the ventricle was seen at  $P_{20}$ , the second at  $P_{25}$ , the third at  $P_{28}$ , and from this point 2:1 heart-block was maintained.









# ON CHYLOUS AND PSEUDO-CHYLOUS ASCITES

BY R. L. MACKENZIE WALLIS AND H. A. SCHÖLBERG

## PART II.<sup>1</sup>

### CONTENTS.

	PAGE		PAGE
Introduction . . . . .	153	Classification . . . . .	168
Abstract of Clinical Notes. Case II . . . . .	153	Aetiology . . . . .	168
General Characters of Fluid No. 3 . . . . .	154	Morbid Anatomy . . . . .	169
Chemical Characters of Fluid No. 4 . . . . .	154	Prognosis . . . . .	171
Physico-chemical Characters of the Fluid . . . . .	159	Physical and Chemical Properties of Pseudo-chylous Ascites . . . . .	172
Abstract of Clinical Notes. Case III . . . . .	159	Chemical Characters . . . . .	173
General Characters of Fluid No. 4 . . . . .	160	Physical and Chemical Properties of Chylous Ascites . . . . .	183
Chemical Characters of Fluid No. 4 . . . . .	160	Chemical Characters . . . . .	183
Physico-chemical Characters of the Fluid . . . . .	163	Conclusions . . . . .	186
Discussion of Results of Chemical Analysis . . . . .	164	Synopses of Cases . . . . .	187
Historical . . . . .	167	Bibliography . . . . .	200

### *Introduction.*

BEFORE comparing the clinical facts and analysis of the case of pseudo-chylous ascites detailed in Part I with those recorded by other writers, we have the good fortune to be able to present two more cases of milky ascites which have since come under our notice. The first comes from a female patient at the Great Northern Hospital, London, admitted under the care of Dr. Horder, and the second from a man under the care of Dr. John Cowan at the Royal Infirmary, Glasgow. Our best thanks are due to these gentlemen for allowing us to publish the cases.

### *Abstract of Clinical Notes of Patient.*

*Case II.* M. S., female, aged 42 years, married. Admitted to the Great Northern Hospital on April 8, 1909, under the care of Dr. Horder, suffering from swelling of the lower extremities and abdomen.

*Past History.* Always healthy until fifteen years ago, when she suffered from white leg after her last confinement. Both legs appear to have been affected. Since then she has always had a certain degree of swelling of the lower extremities. October, 1908, the lower extremities became more swollen,

<sup>1</sup> Part I was published in this *Journal*, vol. iii, 1910, p. 301.



and in December the abdomen was involved. There was no pain, cough, or shortness of breath. The abdomen was first tapped in March, 1909, before admission, and a large quantity of milky fluid withdrawn which reaccumulated, and caused her to come to the hospital for treatment. *Present Condition.* Pale woman, fairly nourished. Oedema of the lower extremities and trunk up to the 8th dorsal spine.—*Chest: Heart.* Apex beat displaced upwards and to the left. Systolic pulsation in the suprasternal notch. Sounds natural. *Lungs* normal, except for evidence of oedema at both bases. *Abdomen.* Circumference 46 inches at the umbilicus: uniformly distended, ascites present: veins round the umbilicus prominent. *Urine.* Diminished in volume, sp. gr. 10.25, acid, cloud of albumin: no sugar, large quantity of urates. April 15, tapped 19.75 pints of milky fluid (received by us next day).

Characters at the time of tapping, supplied by Dr. E. H. Shaw, to whom we wish to express our thanks. Sp. gr. 1.012; alkaline. Microscopically many fine granules which do not stain with Sudan III. A few polymorphonuclear cells and lymphocytes. No parasites or bacteria. Cultures sterile. April 27, tapped again, 19.5 pints (11 litres): abdominal examination showed the liver to be palpable two inches below the costal margin, surface smooth. No growth or induration felt in the abdomen. Tuberculin test negative. May 15, tapped again, 15 pints removed: the fluid seems thinner than on the previous occasion. Temperature subnormal since admission. Left hospital on May 27. No definite clinical diagnosis could be made.

#### *General Characters of Fluid No. 3 (April 27, 1909).*

The fluid was yellowish white, opaque, odourless, and of a homogeneous character. On standing, it showed no traces of a creamy layer, and only a slight deposit could be detected at the bottom of the flask. The fluid did not change in colour or appearance even after standing for several months, and there was no evidence of any putrefactive change taking place. The specific gravity was 1.012 and the reaction to litmus was alkaline. Under the microscope the fluid showed evident refractile fat globules of various sizes, and red blood corpuscles, also some leucocytes (lymphocytes).

Repeated filtration through filter paper did not clear the fluid, but filtration through a Pasteur candle resulted in a clear amber-coloured liquid. Centrifugalization for an hour at 4,000 revolutions per minute produced no apparent change in the opacity of the fluid, though a slight deposit settled at the bottom of the tube, and a dense cream collected on the surface. The addition of ether did not clear the fluid but rather rendered it more opaque: the previous addition of alkali produced a slight reduction of the opalescence. The progressive addition of alkali tended at first to increase the viscosity of the fluid, until finally a condition was reached in which two layers separated out—an upper, semi-solid and opaque in character, and a lower, clear, colourless, and transparent. Chloroform increased the turbidity.

#### *Chemical Characters.*

##### *A. Qualitative.*

(i) *Proteins.* Boiling produced a slight coagulum, and the addition of acetic acid a dense precipitate which filtered with difficulty. Adding an equal

bulk of alcohol led to the formation of a precipitate which on filtration yielded an opalescent fluid, and this on standing showed a fatty scum. Boiling with alcohol in excess gave on filtration a clear fluid which yielded no protein reactions, showing thereby that the total removal of these substances had caused the disappearance of the milky character. Treatment with trichloroacetic acid and boiling gave a dense precipitate and a clear filtrate. The precipitates obtained by the two preceding methods were quite insoluble, and therefore indicated the presence of coagulable proteins. Half-saturation with  $(\text{NH}_4)_2\text{SO}_4$  or full saturation with  $\text{MgSO}_4$  resulted in the production of a dense white precipitate and a very faintly opalescent filtrate, which on full saturation with  $(\text{NH}_4)_2\text{SO}_4$  yielded a perfectly clear filtrate. The opalescent character of the first alcohol filtrate and also the filtrate from half-saturation with  $(\text{NH}_4)_2\text{SO}_4$  was found to be due, not to the serum albumin present, but to a mucinoid substance. The original solution and also the above-mentioned filtrates all gave a partial reduction of Fehling's solution, and also all the characteristic tests for mucinoid, and after removal of this substance the filtrate no longer gave the reduction with Fehling's solution or the usual protein reactions. The fluid showed only traces of fibrinogen according to Hammarsten's method, and this substance gave only a very slight turbidity when treated with fibrin ferment prepared from blood plasma. Digestion experiments showed the absence of any purin bodies, and hence the fluid was free from nucleo-proteins.

(ii) *Fats, lecithin, and cholesterol.* The demonstration of the presence of fat was difficult owing to the anomalous behaviour of the milky fluid when treated with ether. Extraction with ether extending over several weeks led to the formation of two distinct layers—an upper dense white creamy layer which was almost semi-solid, and a lower turbid yellow layer. The creamy layer contained the fat, lecithin, and protein as shown by qualitative tests. The fat present could not be extracted in the presence of these substances, so that another procedure was necessary. The precipitate obtained by boiling with alcohol was collected and repeatedly extracted with boiling alcohol. The original filtrate and the alcohol washings were evaporated down to a small bulk and then extracted with ether. The ether extract was treated with acetone and gave a white deposit of lecithin which was removed. The resulting filtrate was evaporated to dryness and yielded a brownish yellow oily mass which set to a solid at about  $30^\circ\text{C}$ . and melted at  $40^\circ\text{C}$ . This residue for the greater part consisted of neutral fat, non-crystalline, and with a melting-point of (*circa*)  $38^\circ\text{C}$ . There were also traces of free fatty acids present. The residue was tested for cholesterol with a negative result.

(iii) *Carbohydrates.* Application of the usual sugar tests, both to the original fluid and also to the fluid after removal of the proteins, gave negative results, the partial reduction of Fehling's solution being due to the presence of mucinoid material.

(iv) *Other Organic Substances.* The presence of urea in the fluid was demonstrated after the proteins had been removed by trichloroacetic acid, the

slight effervescence with sodium hypobromite revealing only traces of this substance. Uric acid, bile pigments, and bile acids were absent, as also were glycogen, creatin, creatinin, and amino acids. The biuret test for albumoses and peptones gave a negative result.

(v) *Inorganic salts.* Chlorides, phosphates, sulphates, sodium, potassium, calcium, magnesium, and traces of iron were detected.

(vi) *Ferments.* Proteolytic ferments and amylolytic ferments were found to be absent, but the fluid contained a lipase.

### B. Quantitative.

(i) The total solids calculated on 50 cubic centimetres of the fluid gave a figure of 2.422 grammes, and therefore 4.844 grammes per cent. The residue was of a dark grey colour, having an odour of burnt fat. The ash residue on incineration yielded a figure of 0.366 gramme or 0.732 gramme per cent.

(ii) The degree of alkalinity, using methyl orange as an indicator and  $\frac{N}{10}$   $H_2SO_4$ , was 0.177 per cent. in terms of NaOH.

(iii) The total protein content was 2.058 grammes per cent., as determined by precipitation with alcohol, and repeated washing with hot alcohol, drying, and weighing. The residue obtained by boiling 60 cubic centimetres with trichloroacetic acid gave a figure of 1.121 grammes or 2.242 grammes per cent. This residue was further treated with hot alcohol, and then dried and weighed, and now gave 1.029 grammes or 2.058 grammes per cent. Therefore the alcohol had removed 0.184 gramme per cent. from the residue precipitated by trichloroacetic acid, which may represent part of the lecithin and fat. The residue insoluble in alcohol was decomposed with fusion mixture and still gave a phosphorus reaction.

*Precipitation by ammonium sulphate.* 200 cubic centimetres of the fluid were treated with an equal bulk of a saturated solution of  $(NH_4)_2SO_4$ , shaken and allowed to stand for twenty-four hours. A dense white precipitate separated in the form of a creamy layer on the surface and the lower layer was slightly opalescent. The precipitate was separated by filtration and suspended in water, giving a strongly opalescent solution. This suspension entirely cleared when reprecipitated with ammonium sulphate, and gave an opalescent solution on re-solution. By repeated precipitation and re-solution a white residue was obtained which only partially dissolved in dilute saline solutions, and in appearance resembled the opacity of the original fluid. The white residue gave on fusion a well-marked phosphorus reaction. The remaining portion of the residue was treated with hot alcohol until the residue no longer gave a phosphorus reaction. From the alcohol washings a residuum was obtained which gave the test for phosphorus, and when treated with barium hydrate and evaporated to small bulk yielded an alcoholic extract which contained choline. The choline was isolated as the crystalline platinum salt. The presence of lecithin in this residue was thus demonstrated, and by treatment with hot alcohol it could be removed, leaving the residue entirely phosphorus free. The serum

globulin, estimated quantitatively after precipitation with  $(\text{NH}_4)_2\text{SO}_4$  and extraction with alcohol, amounted to 0.693 gramme per cent.

After removal of the serum globulin the opalescent filtrate was fully saturated with  $(\text{NH}_4)_2\text{SO}_4$ , and the resulting precipitate suspended in distilled water. The solution was opalescent, but the addition of acetic acid served completely to remove the opalescence, and a very fine flocculent precipitate was noted. This precipitate was with difficulty removed, and gave on analysis a reduction of Fehling's solution, and proved to be mucinoid. The filtrate after removal of the mucinoid gave a coagulum on boiling which, when dried and weighed, amounted to 1.296 grammes per cent. The serum globulin content of the fluid was 0.693 gramme and the serum albumin content 1.296 grammes; the ratio of albumin to globulin is therefore as 1.86 : 1. The remaining protein, consisting of the mucinoid substance present, was 0.069 gramme by difference, a figure which curiously enough was identical with that recorded in the table for pseudo-chylous fluid No. 2 (*vide* Part I). The figure for the total nitrogen was 0.462 gramme per cent., and for the residual nitrogen was 0.011 gramme per cent. Arising out of the quantitative estimation of the different proteins the following observations are of considerable interest. A portion of the original milky fluid filtered through a Pasteur candle resulted in a clear filtrate which in appearance resembled ordinary ascitic fluid, which gave the following reactions:—

The addition of alcohol or acetic acid yielded precipitates on boiling; but half-saturation with  $(\text{NH}_4)_2\text{SO}_4$  gave no precipitate. Acetic acid alone gave no precipitate, and there was no reduction of Fehling's solution, showing the absence of the mucinoid substance. The protein present gave all the characteristic reactions for serum albumin. The total nitrogen content of this filtrate was 0.2184 gramme per cent., which includes the residual nitrogen with the albumin nitrogen. The residue on the candle was extracted with water, and the resulting suspension was phosphorus free. The material remaining on the candle was now repeatedly treated with hot alcohol, and the washings showed the presence of a white precipitate. This was isolated, and gave the faintest traces of phosphorus. The alcohol filtrate was evaporated to dryness and showed the presence of lecithin. The residue on the candle therefore consisted of the globulin, the mucinoid, the fat and the lecithin, and the mechanical removal of these substances was associated with the disappearance of the opalescence.

*Fat and lecithin.* For extraction of these substances 250 cubic centimetres were treated with ether and shaken repeatedly for several days. The fluid showed at the end of this period a marked clearing owing to the separation of a dense creamy upper layer. The lower stratum was quite fluid, and of a yellowish colour, with a slightly opalescent appearance. This was separated, and found to measure (*circa*) 210 cubic centimetres. Extraction of this fluid with ether gave a negative result, and the fluid was unaltered in appearance. Evaporation to dryness at  $100^\circ\text{C}$ . gave a figure for the total solids of 2.240 grammes per cent. and this on incineration gave 0.720 gramme of ash. Since the total solids amount to 4.844 grammes per cent., and the ash of this to 0.732

gramme, by difference the creamy layer contained 2.604 grammes of solids, with an ash figure of 0.012 gramme. The fluid portion on analysis was found to contain the serum albumin, and only traces of serum globulin, but no mucinoid material or fat. The semi-solid creamy layer was then extracted with hot ether for several days, and the residue was found to contain serum globulin and mucinoid material. For the estimation of the fat and lecithin the original fluid was extracted with strong alcohol, and the alcoholic extract evaporated to a small bulk, and then treated with ether. The ether extract so obtained gave a deposit when treated with acetone, which weighed 0.360 gramme per cent., and was identified as lecithin. This residue was treated according to Neumann's method as modified by Bayliss and Plimmer, and yielded 0.00319 gramme  $P_2O_5$ , and this is equal to 0.00139 gramme of phosphorus. The lecithin present in this fluid was undoubtedly distearyl-lecithin. The ether acetone extract remaining after removal of the lecithin was evaporated to dryness on a water bath, and weighed 1.501 grammes per cent., which was the total amount of fat present in the fluid, since cholesterin or cholesterin esters were absent.

*Inorganic salts.* The quantitative analysis was carried out in two ways.

(i) The ash obtained from 100 cubic centimetres of the fluid was dissolved in distilled water, and made up to 100 cubic centimetres. The solution so obtained was alkaline in reaction, and the degree of alkalinity expressed in terms of  $\frac{N}{10}H_2SO_4$  was 18.0 per cent. The solution of the ash (0.732 gramme) gave on analysis 0.580 gramme of chlorides (estimated as sodium chloride), 0.036 gramme of  $P_2O_5$ , and 0.002 gramme of  $SO_3$ .

(ii) 200 cubic centimetres of the original fluid were placed in a sausage dialyser, and immersed in 400 cubic centimetres of pure distilled water. The dialyser was kept in continuous motion for several hours, and at a constant temperature of  $12^\circ C$ , and at the end of the experiment the volumes of the fluids had not appreciably changed. The dialysed residue was very opalescent, but on standing a white precipitate settled out as a creamy layer with a considerable reduction in the opalescence. The reaction of the residual fluid was alkaline to litmus, and the alkalinity corresponded to 9 per cent.  $\frac{N}{10}H_2SO_4$ . Specific gravity 1.009. The total solids amounted to 3.184 grammes per cent., and this gave an ash figure of 0.126 gramme. The ash soluble in water was 0.116 gramme, leaving an insoluble ash figure of 0.010 gramme. The soluble ash proved on analysis to contain 0.102 gramme per cent. of chlorides and 0.009 gramme of  $P_2O_5$ . The insoluble ash gave an  $SO_3$  figure of 0.001 gramme per cent.

The dialysate was quite clear, and showed no traces of protein. The specific gravity was 1.0025, and the reaction alkaline. The alkalinity corresponded to 9 per cent.  $\frac{N}{10}H_2SO_4$ . On analysis the dialysate was found to contain 0.476 gramme of chlorides, 0.0304 gramme  $P_2O_5$ , and 0.001 gramme  $SO_3$  per cent.

*Physico-chemical Characters of the Fluid.*

The acid binding power of the fluid was determined in the following way. 50 cubic centimetres of the fluid required 20.7 cubic centimetres of  $\frac{N}{10}$   $H_2SO_4$  for neutralization when methyl orange was used as an indicator. A known quantity of standard acid was then added, and the total titrated with  $\frac{N}{10}$   $NaOH$  until neutrality was again reached. It was then found that 0.8 c.c. of the acid had combined with the protein present, and this figure compares very favourably with that obtained for serum.

The fluid was exposed to radium rays, as in the previous fluids examined (*vide* Part I), for forty-eight hours, and a white deposit was noted with considerable clearing of the fluid. The milkiness of the fluid, however, was not entirely removed, and the opacity was comparable to the fluid after dialysis.

The freezing-point determination, using Beckmann's apparatus, gave an average depression of  $0.56^\circ C$ . (Ascitic fluid figure was  $0.59^\circ C$ .)

*Abstract of the Clinical Notes of Patient from whom Fluid No. 4  
was obtained.*

*Case III.* R. C., male, aged 61. Admitted, March 3, 1910, to the Glasgow Royal Infirmary under the care of Dr. John Cowan, suffering from swelling of the legs and abdomen.

*History of the present illness.* About twelve months ago the patient noticed that he passed an increased amount of urine. He had no headache, sickness, or constipation. About five weeks ago his hands and arms became swollen, but this passed off in a week or so. Soon after the legs began to swell and later the scrotum and abdomen, and the patient was confined to his bed. There was shortness of breath and orthopnoea. *Past Illness.* Always healthy except for an illness he had twelve years before, when he was off work for twelve months. He then suffered from pain in the abdomen, and the complaint terminated with the formation of an abscess, which ruptured anteriorly in the left hypochondriac region, healed slowly, and left a painless indurated scar. *Present condition.* Well-built man, poorly nourished, feeble muscular development. There was a well-marked oedema of the lower extremities and trunk. Temp.  $98.0^\circ F$ . *Circulatory System.* Pulse 70, tension high (170 mm.). Regular Heart. Left ventricle hypertrophied. No murmurs. Aortic sound intoned. *Respiratory System.* Respirations 20 per minute: bubbling râles all over the back, and deficient air entry at the right base. *Urinary System.* March 2, Sp. gr. 1.025. Reaction acid. Smoky colour. Large quantity of albumin, 6 per cent. Cellular and granular casts. No sugar, bile, or indican. May 11, Sp. gr. 1.008. Acidity 23.2 per cent.  $\frac{N}{10}$   $NaOH$ . Albumin 0.2 per cent. Chlorides 0.47 per cent. Phosphates 0.075 per cent.

After admission the patient improved, the urinary output was increased, and the oedema lessened. The ascitic fluid removed on March 14 was centrifugalized, and showed on microscopical examination a deposit consisting mainly of degenerated mononuclear cells and a few red cells. Differential count made from stained films (Dr. A. W. Harrington) reads as follows:—Lymphocytes

51 per cent. Large mononuclear 42 per cent. Endothelial cells 6 per cent. Polymorphonuclear 1 per cent.

The blood serum of the patient was quite clear. The Wassermann reaction was negative. In May the patient suffered from catarrh of the chest, diarrhoea and increased haematuria, but recovered. The ascites, however, had to be tapped frequently, on which occasions the liver on palpation appeared harder than normal, though it was impossible to recognize any alteration in the size of the organ. During June the patient improved considerably, and finally left the Institution on July 30, 1910. A provisional diagnosis of cirrhosis of the liver was made.

#### *General Characters of Fluid No. 4 (April 5 and 9).*

A white milky fluid in appearance resembling the fluid No. 1, described in Part I of this paper, with the possible difference that it was not quite so opaque. On standing a very scanty deposit separated out, and there was only the merest trace of a creamy layer on the surface. The fluid, however, when stored for some time, cleared partially, the process resembling the gradual settling of a fine suspension of china clay. Chloroform was added as a preservative, and the fluid kept perfectly fresh for several months. The specific gravity of the fluid was 1.008, and the reaction to litmus alkaline. Under the microscope the fluid showed no evident fat globules, and resembled in every particular fluid No. 1 described in the previous communication. Filtration through filter paper did not clear the fluid, but when passed through a Pasteur candle a clear, almost colourless filtrate was obtained. Centrifugalized the fluid became quite clear, and a dense white precipitate had settled at the bottom of the tube, with the merest trace of a cream upon the surface. Treatment of the fluid with ether did not alter the opalescence, but the previous addition of caustic potash rendered the fluid perfectly transparent. Chloroform tended to increase the opalescence.

#### *Chemical Characters.*

##### *A. Qualitative.*

(i) *Proteins.* Boiling produced no coagulation, but on acidification with acetic acid a white flocculent precipitate settled down, leaving the supernatant fluid quite clear. Addition of alcohol, picric acid, alkaloidal reagents, and other protein precipitating reagents had a similar effect. Glacial acetic acid and caustic soda both removed the opacity of the fluid, and with the latter reagent the fluid became reddish brown. The original fluid gave all the protein colour reactions.

The precipitates obtained by heating the fluid with an excess of alcohol, and also by trichloroacetic acid, were quite insoluble in water, and the filtrates in both cases quite free from proteins, albumoses, or peptones. Half-saturation with  $(\text{NH}_4)_2\text{SO}_4$  or saturation with  $\text{MgSO}_4$  resulted in the deposition of a white precipitate, leaving the fluid quite clear and colourless. The residue was only partially soluble in dilute saline solutions and gave a well-marked

phosphorus reaction. The clear filtrate contained a coagulable protein, which could be separated by full saturation with  $(\text{NH}_4)_2\text{SO}_4$ , and behaved in every way similar to serum albumin. It contained no phosphorus, and was soluble in water. When large quantities of the fluid were taken traces of mucinoid could be separated, and its presence in such small quantities had no effect on the opalescence of the fluid. Neither fibrinogen nor nucleo-proteins were present.

(ii) *Fats and lecithin.* Extraction of the fluid with ether for several days resulted in a very slight clearing of the fluid, a white precipitate accumulating at the junction of the two liquids. The removal of the ether extract left the fluid almost as opalescent as the original, and, further, the fluid showed no tendency to settle as in the case of the original solution. The ether extract was evaporated to a small bulk, and then treated with acetone, the resulting waxy deposit being slightly pigmented, possibly owing to the presence of a small quantity of lipochrome in the fluid. The fat in solution was obtained in the form of a dark yellow oil when the ether-acetone solution was evaporated to dryness. From this oily residue on cooling a white solid fat with a melting-point of  $44^\circ\text{C}$ . separated. Cholesterin tests on the original fluid and also on the ether extract were negative.

(iii) *Carbohydrates.* Testing the original fluid with Fehling's solution gave a complete reduction. Positive results were also obtained with the Trommer, Moore, safranin, and sulphindigotate (Mulder) tests. The proteins were removed from the fluid by boiling with an excess of alcohol, and the alcoholic solution evaporated to dryness on a water bath. A watery extract of the alcohol residue gave all the tests for sugar. A portion of the extract was treated in the usual way for the preparation of osazone crystals, and a crystalline deposit of yellow-coloured needles resembling dextrosazone recognized microscopically. In their solubility and melting-point they proved to be dextrosazone. It was found, however, that if the proteins were removed by simple precipitation with alcohol or trichloroacetic acid, the protein-free solution gave negative tests for sugar. The same occurred when the fluid was passed through a Pasteur candle.

(iv) *Other organic substances.* The same products as enumerated above, were absent, as also was urea.

(v) *Inorganic salts.* Chlorides, phosphates, sulphates, sodium, potassium, calcium, magnesium, and traces of iron were present.

(vi) *Ferments.* Testing by the methods already described, no evidence of ferments could be found in the fluid.

### B. Quantitative.

(i) For the estimation of the total solids 100 cubic centimetres were taken, and yielded a yellowish white residue with a biscuit-like smell, which weighed 1.532 grammes. The ash residue from this gave a figure of 0.775 gramme.



(ii) The alkalinity, using methyl-orange as an indicator and  $\frac{N}{10}$   $H_2SO_4$ , was 0.156 per cent. in terms of NaOH.

(iii) The total protein content was 0.5132 gramme per cent., as determined by precipitation with hot alcohol, and repeated washing of the precipitate with hot alcohol. The precipitate after treatment with trichloroacetic acid weighed 0.844 gramme and included the sugar, fat, and lecithin. The residue after repeated washing with alcohol was treated by the Asboth-During method for organic sulphur, and gave on analysis 0.0288 gramme per cent. of organic  $SO_3$ . The total ash from the coagulable proteins amounted to 0.1096 gramme per cent., and contained 0.002 gramme of  $P_2O_5$ . The ash-free protein content was therefore 0.4036 gramme per cent.

*Precipitation by ammonium sulphate.* 500 cubic centimetres of the fluid were taken, and an equal bulk of saturated ammonium sulphate added. The white precipitate which resulted filtered quite readily, but was only very partially soluble in dilute saline solution. The washings were collected together, and the soluble protein reprecipitated, dried, and weighed. The soluble globulin was quite free from lecithin, and amounted to 0.082 gramme per cent. The insoluble portion of the precipitate after repeated washings with distilled water was extracted with ether. The ether extract yielded a phosphorus-containing substance in very small quantity. The residuum was, however, found to be more soluble in dilute saline solution, and gave all the reactions of serum globulin. The most striking feature was its ready solubility in very small quantities of saline, and this after treatment with ether. The insolubility of the serum globulin in this fluid seems to be determined by its association with lipine material. The residue after extraction with ether weighed 0.2152 gramme per cent. The total globulin content was, therefore, 0.2972 gramme. The clear filtrate, after removal of the globulin and its associated lipine, was subjected to full saturation with ammonium sulphate, and gave a white precipitate of serum albumin, which was soluble in water and coagulated on heating. When dried, it weighed 0.216 gramme per cent. The total nitrogen figure was 0.1316 gramme per cent.

*Fat and lecithin.* 250 cubic centimetres were extracted with ether, and gave on analysis 0.0064 gramme per cent. of lecithin and 0.1004 gramme per cent. of fat. Extraction of the original fluid with hot alcohol yielded a clear filtrate, which gave a precipitate of lecithin weighing 0.0228 gramme per cent. This residue, on hydrolysis with barium hydrate, gave typical crystals of choline platinochloride. The total  $P_2O_5$  in the alcohol filtrate amounted to 0.028 gramme per cent., this figure including the inorganic and also the organic phosphorus. The organic  $P_2O_5$ , as recorded above amounted to 0.002 gramme, a figure agreeing with the calculated  $P_2O_5$  in the lecithin content of the fluid. The total lecithin present was, therefore, in association with the serum globulin, and ordinary ether extraction was able only to remove the merest trace, viz. 0.0064 gramme. Hot alcohol on the other hand removed the lecithin, and left the serum-globulin phosphorus free.

*Carbohydrates.* The sugar present in the fluid was extracted with alcohol, and the alcoholic extract made up to a definite volume with distilled water. An estimation by Ling's method revealed the presence of 0.196 gramme per cent. of sugar, and by Citron's method 0.186 gramme per cent. After dialysis the dialysate was found to contain 0.087 gramme per cent. of sugar, showing that 0.109 gramme per cent. of the sugar was still in combination.

*Inorganic salts.* The analysis was carried out quantitatively in three ways.

(i) The ash from 100 cubic centimetres of the fluid was dissolved in distilled water, and made up to 100 cubic centimetres. 0.775 gramme of ash gave on analysis 0.71 gramme of chlorides estimated as sodium chloride, 0.028 gramme of  $P_2O_5$ , 0.0029 gramme of  $SO_3$ , 0.006 gramme of calcium as phosphate, and traces of iron.

(ii) The proteins were removed from the fluid by an excess of boiling alcohol, and the alcoholic extract evaporated to dryness on a water bath. This residue gave on analysis 0.71 gramme of chlorides, 0.028 gramme of  $P_2O_5$ , and traces of sulphates.

(iii) 200 cubic centimetres of the fluid were placed in a dialyser as above described, and surrounded by 400 cubic centimetres of distilled water. After twenty-four hours' dialysis the fluid in the dialyser was found to be quite clear, and of a pale amber colour. The white deposit which had separated out at the bottom of the parchment tube proved on analysis to contain globulin and lecithin. It weighed 0.3136 gramme per cent. The clear supernatant fluid showed only traces of globulin, but contained serum albumin and a small quantity of sugar. The slightly opalescent dialysate measured approximately 380 cubic centimetres, was alkaline, and had a specific gravity of 1.004. The alkalinity, using methyl-orange as an indicator and  $\frac{N}{10} H_2SO_4$ , was 23.2 per cent.

The dialysate was free from proteins and lecithin. An analysis of the dialysate gave the following figures, which for convenience are calculated in percentages of the original solution, and consequently represent the constituents which are removable by dialysis: 0.0870 gramme of sugar, 0.56 gramme of chlorides, 0.0240 gramme of  $P_2O_5$ , sulphates in traces. A comparison of the analysis of this fluid with those recorded reveals the fact that the salts present were almost identical both in quantity and in the nature of their distribution in the two fluids. The most striking difference is the large quantity of chlorides in this fluid as compared with the fluid No. 2 analysed in the previous paper.

#### *Physico-chemical Characters of the Fluid.*

In order to determine the relationship of the salts present to the proteins the following procedure was adopted. The original fluid when titrated with  $\frac{N}{10} H_2SO_4$ , and using methyl-orange as an indicator of the neutrality point,

required 40.6 cubic centimetres for 100 cubic centimetres of the fluid. To this solution a known volume of  $\frac{N}{10}$   $H_2SO_4$  was added, and then titrated back with  $\frac{N}{10}$  NaOH. The amount of alkali required for neutralization was noted, and it was found that 1.6 cubic centimetres of the acid were combined with the protein. The resulting fluid was now placed in a dialyser with an equal volume of distilled water surrounding it, and left for several hours. The fluid was now alkaline and required 0.4 cubic centimetre of  $\frac{N}{10}$   $H_2SO_4$  for neutralization. The dialysate from 200 cubic centimetres of the original fluid required 23.2 cubic centimetres of  $\frac{N}{10}$   $H_2SO_4$ , and the dialysed residue 17 cubic centimetres of  $\frac{N}{10}$   $H_2SO_4$ . The solution of the ash obtained from 100 cubic centimetres of the original fluid required 29 cubic centimetres of  $\frac{N}{10}$   $H_2SO_4$  with methyl-orange, and 17 cubic centimetres when phenol-phthalein was used as an indicator. Comparing the results obtained in this way with those of the fluids previously described we have:—

		$\frac{N}{10}$ $H_2SO_4$	$\frac{N}{10}$ $H_2SO_4$
		Methyl-orange.	Phenol-phthalein.
Original fluid (No. 4)	. . .	40.6%	
" " (No. 3)	. . .	43.4%	19.4%
Dialysate " (No. 4)	. . .	23.2%	
" " (No. 3)	. . .	36.0%	9.9%
Ash " (No. 4)	. . .	29.0%	17.0%

The figures show very clearly the influence of the colloidal proteins on the alkalinity of the fluid as determined by the ordinary titration methods.

#### *Discussion of Results of Chemical Analysis of the Fluids Nos. 3 and 4.*

The fluids from Case II and from Case III show the same general characters. The fluid removed at subsequent tapplings was always of a greater opacity, and contained more fat. The same observations as regards the general properties of these fluids hold as for those described in Part I of this paper. Filtration through a Pasteur candle entirely removed the opalescence, and in fluid No. 4 centrifugalization produced a similar effect. Of the proteins present, the serum globulin occurs in the fluid in association with lecithin. The lecithin can be removed by treatment with hot alcohol, but only with great difficulty when ether is substituted. The serum globulin with its associated lipine does not give the ordinary reactions for globulin, but when the lipine is removed by ether the solubility of the globulin is very characteristic. The opalescence is entirely due to this complex in fluid No. 4, and almost entirely in fluid No. 3. The degree of opalescence depends upon the amount of globulin

lecithin present. Only a very small quantity of globulin is free from lipine in fluid No. 4, and in fluid No. 3 the globulin is fully combined.

With the exception of the presence of mucinoid in No. 3, the fluids are quite free from other proteins, e.g. nucleo-proteins, and also albumoses and peptones. The presence of sugar in fluid No. 4 is of interest from the fact that in all the other fluids no traces could be found. This sugar is dextrose, and its presence is very significant. The clear filtrate after removal of the lecithin-globulin complex by passage through a Pasteur candle is quite free from sugar, as is the filtrate after precipitation of the proteins by trichloroacetic acid. As a control experiment it was found that the dextrose present in blood serum behaves in a similar way. Ordinary ox-serum passed through a Pasteur candle shows no sugar in the filtrate, whereas the serum before treatment contains this substance. This observation cannot be further discussed now, and will be dealt with at a future date.

The fat in these fluids behaves in every way like pathological fat, i.e. degeneration fat. In its melting-point and its physical and chemical properties it approaches the stearic group of fats.

We would again call attention to the power these fluids possess of resisting putrefaction, and this is probably due to the presence of lecithin. The lecithin present is all in combination with the globulin in both the fluids, which renders this fact all the more striking. The absence of cholesterin should also be noted. Of the nitrogenous extractives urea was demonstrated in the first fluid only, and then but traces were present.

The two most important inorganic constituents as before were the chlorides and phosphates. In the case of the chlorides the second case showed a much larger quantity than the first; in fact the bulk of the ash consisted of this salt. The quantity which was dialysable was proportionally very much smaller than in the fluids previously described. The phosphates in both fluids were very similar in quantity and closely approximated the amounts in the previous analyses.

TABLE I. *Showing Analysis of the Milky Fluids from Cases recorded in Parts I and II.*

	Fluid No. 1, 10.5 litres (Case I).	Fluid No. 2, 11.36 litres (Case I).	Fluid No. 3, 11.0 litres (Case II).	Fluid No. 4, several litres (Case III).
Nature . . . . .	Milky white	Dense milky white and creams on standing	Yellowish white	Pale milky white
Specific gravity . .	1.010	1.012	1.012	1.008
Degree of alkalinity	0.152 % NaOH	0.152% (approx.)	0.177 %	0.156 % NaOH
Depression of freez- ing-point . . . .	-0.59° C.	-0.61° C.	-0.56° C.	-0.60° C.
Total solids . . .	2.520	2.741	4.844	1.532
Ash . . . . .	0.780	0.780	0.732	0.775
Proteins. Total . .	0.652	1.220	2.058	0.5132
Serum albumin . .		0.490	1.296	0.216
Serum globulin . .		0.671	0.693	0.2972
Mucinoid . . . .	traces	0.069	0.069	traces
Ratio of albumin to globulin . . . . .	—	1:1.8	1.86:1	1:1
Total nitrogen . .		0.490 (?)	0.462	0.1316
Fat . . . . .	0.8140	0.603	1.501	0.1004
Lecithin . . . . .	0.274	0.128	0.360	0.0228
Cholesterolin . . .	absent	absent	absent	absent
Sugar . . . . .	absent	absent	absent	0.196 (Ling's method) 0.186 (Citron's method)
Urea . . . . .	absent	absent	traces	absent
Chlorides. Total . .	0.603	0.593	0.580	0.71
Phosphates (P <sub>2</sub> O <sub>5</sub> ). Total . . . . .		0.028	0.036	0.028
Sulphates (SO <sub>3</sub> ) . .		0.0294	0.002	0.0029
Calcium oxide . . .	0.025	0.017	0.002	0.006 (Ca <sub>3</sub> PO <sub>4</sub> )
Iron . . . . .	traces	traces	traces	traces
Diamines . . . . .	traces	traces	—	—
Creatin . . . . .	absent	absent	absent	absent
Creatinin . . . . .	absent	absent	absent	absent
Uric acid . . . . .	absent	absent	absent	absent

TABLE II. *To illustrate the Condition of the Inorganic Constituents and Sugar in the Fluids.**Fluid No. 2 (see Part I, p. 309).*

	Ash.	Alcohol Filtrate.	Dialysate.
Total . . . . .	0.780	0.492	
Chlorides . . . . .	0.593	0.420	0.589
Chlorides, Free . . . .		(0.420)	(0.589)
Chlorides, Combined . .		(0.173)	(0.004)
Phosphates (P <sub>2</sub> O <sub>5</sub> ). Total .	0.028	0.028	0.0195
Inorganic . . . . .			0.0195
Organic . . . . .		(0.0096)	(0.0085)
Sulphates (SO <sub>3</sub> ) . . . .			
Inorganic . . . . .			
Organic . . . . .			
CaO . . . . .	0.017		

TABLE II (*continued*).*Fluid No. 3* (see p. 158).

	Ash.	Alcohol Filtrate.	Dialysate.
Total . . . . .	0.732		
Chlorides. Total . . . . .	0.580		0.476
Chlorides, Free . . . . .	0.476		
Chlorides, Combined . . . . .	0.102		
Phosphates ( $P_2O_5$ ). Total . . . . .	0.0360	0.036	0.0304
Inorganic . . . . .	0.0304		
Organic . . . . .	(0.002)	0.002	
Sulphates ( $SO_3$ ). . . . .	0.002		0.001
Inorganic . . . . .	0.001		
Organic . . . . .	0.001		

*Fluid No. 4* (see p. 163).

	Ash.	Alcohol Filtrate.	Dialysate.
Total . . . . .	0.775		
Chlorides . . . . .	0.71	0.71	0.56
Chlorides, Free . . . . .	0.56		
Chlorides, Combined . . . . .	0.15		
Phosphates ( $P_2O_5$ ). Total . . . . .	0.028	0.028	0.024
Inorganic . . . . .	0.0278		
Organic . . . . .	0.0022		
Sulphates ( $SO_3$ ). Total . . . . .	0.029		
Inorganic . . . . .	(0.001)		
Organic . . . . .	0.0288	0.0288	(below 0.001)
Sugar . . . . .		{ 0.196 } { 0.186 } Two methods	0.0870

*Historical.*

The appearance of a milky ascitic fluid is such a striking phenomenon that it could hardly escape notice, and it is therefore not surprising that records of cases are to be found in the older writers. That a milky effusion could occur as the result of trauma was long known, but that such could also appear as the result of disease was first established by Morton (13), Vernage, and others nearly 250 years ago. There is no necessity to trace the varying kinds of clinical cases in which milky effusions were chronicled by earlier observers, for they have been fully detailed in the monographs of Jousset (67), and Poupy,<sup>2</sup> and in the papers of Bargebuhr (29), Boston (34), Batty Shaw (112), and Busey (125). Previous to 1860 there were recorded twenty-five cases of milky peritoneal effusions, and during the last fifty years we have traced 171 cases, including the three which are submitted in this paper. They are tabulated in chronological order (pp. 187-96). A few have been omitted, as the details published are insufficient, and others have probably escaped our notice, but the list is as complete as we have been able to make it. It should be added that milky effusions due to parasitic infections have not been included.

<sup>2</sup> *Thèse*, Paris, 1898.

*Classification.*

A rigid differentiation of the different kinds of milky effusions to be found in the peritoneal and other serous cavities has always presented considerable difficulty. Quinke (106) was the first to put forward a classification which recognized two types of fluid, an hydrops chylosus and an hydrops adiposus. Later, he included a third type which has since been called pseudo-chylous. Hydrops chylosus includes all effusions into the serous cavities in which there is direct anatomical evidence pointing to an implication of the lacteal and lymphatic systems. Hydrops adiposus furnishes examples of milky fluids in which the fat present is derived from degenerated cells and not from the addition of chyle. This classification was based on the view that the milkiness of these effusions was due to fat and fat only, provided the degree of subdivision was sufficiently minute. It was found, however, that a milky character could arise from the presence of substances other than fat, and to include such Quinke accepted the term pseudo-chylous. Ceconi (40), in writing on the subject, differentiated three forms, chylous, chyloform, and mixed effusions, the last containing varying amounts of chyle. Pagenstecher (99) held the view that in addition to true chylous effusions there were fluids in which the milky appearance was due to (a) fatty degeneration of cells, (b) inflammatory changes, or (c) chemical substances of a non-fatty nature. Later in 1907 Massing (83) supported the classification of Quinke, but contended that the pseudo-chylous type of effusion could not be satisfactorily differentiated from the two main groups first introduced by Quinke. The classification adopted by H. D. Rolleston<sup>3</sup> and accepted by most writers is a modification of that introduced by Quinke and recognizes three groups, chylous, chyloform, and milky, non-fatty effusions. This corresponds on the whole with the view that the fat present is the chief criterion indicative of a milky effusion, and that where this does not obtain the fluid under consideration falls into the third category. Now chyloform effusions are frequently such, not because of the fat that may be present in considerable amount, but by reason of some other substance which is identical with that causing the opalescence in milky, non-fatty effusions. The two groups then are hardly distinct enough to justify a main heading. They should rather be classified as varieties of one type, which may be called pseudo-chylous. Chylous effusions would include as before those due to trauma or to the escape of chyle in diseases affecting the lacteal and lymphatic systems. The chemical data supporting this classification will be given later.

*Ætiology.*

The local and general causes are similar to those for ordinary ascites, but why the effusion should possess the constituents which endow it with a milky appearance is unknown. Direct lesions of the thoracic duct or of the lacteal

<sup>3</sup> Osler and McCrae, *System of Medicine*.

and lymphatic system, giving rise to a leakage from the chyle vessels, afford an explanation of a certain number of cases. When, however, a case of cirrhosis of the liver, which usually is found associated with a clear serous fluid, yields a milky effusion due to a lecithin-globulin complex, the reason why such a substance has appeared is susceptible of no explanation at present.

*Age incidence.* This is best shown by giving the incidence at different ages, the figures being taken from 145 cases which appear in the synopsis of recorded cases.

Under 1 year	.	.	.	.	.	.	.	.	3 cases
From 1-10 years	.	.	.	.	.	.	.	.	8 "
" 10-20 "	.	.	.	.	.	.	.	.	17 "
" 20-30 "	.	.	.	.	.	.	.	.	18 "
" 30-40 "	.	.	.	.	.	.	.	.	24 "
" 40-50 "	.	.	.	.	.	.	.	.	24 "
" 50-60 "	.	.	.	.	.	.	.	.	29 "
" 60-70 "	.	.	.	.	.	.	.	.	22 "
Total									145

It will be seen that seventy-seven of the cases occur between the ages of 30 and 60 years, and that more than two-thirds lie between the thirtieth and seventieth years of life. The maximum incidence appears between the ages of 40 and 60 years. Boston (34) in a record of 126 cases found that the condition was most frequent between the ages of 30 and 50, the highest figure of incidence appearing at the thirty-fifth year of life. From the above table there would seem to be a steady increase up to the sixtieth year.

*Sex incidence.* Of the 145 cases in which sex was given 74 were males and 71 females, showing an almost equal distribution between the two sexes. Boston (34) gives a slight preponderance to the female sex, namely 61 cases to 50 males out of a total of 111.

### *Pathology. Morbid Anatomy.*

The conditions found in milky ascites are various, no one lesion being characteristic of the condition. The following table presents the chief morbid changes found in the cases tabulated, whether they be chylous or pseudo-chylous :—

#### A. Tumours.

1. Carcinomata of abdominal organs . . . . .	56
(Stomach 21, ovary 10, pancreas 6, peritoneum 5, large intestine 4, gall bladder 2, liver 1, uterus 1, abdominal growths of uncertain origin 6.)	
2. Carcinoma of the pleura . . . . .	1
3. Sarcoma of abdominal organs . . . . .	19
(Lymphosarcoma 12, sarcoma of ovary 3, mesentery 2, pelvis 2.)	
4. Lymphadenoma . . . . .	4
5. Lymphangioma . . . . .	1
Total . . . . .	81

#### B. Infections.

6. Tuberculosis . . . . .	33
(Peritonitis, pulmonary, generalized miliary tuberculosis, lymphatic.)	
7. Chronic peritonitis . . . . .	9
8. Syphilis . . . . .	3
9. Cellulitis . . . . .	1
Total . . . . .	46



## C. Affections of the thoracic duct and lymphatic system.

10. Obstruction of the thoracic duct . . . . .	19
(Thrombosis 1, by growths 7, duct cancerous throughout 11.)	
11. Rupture of the thoracic duct . . . . .	4
12. Compression and distension of lymphatics or chyle vessels . . . . .	14
13. Trauma: 3 direct injury, 1 post-operative . . . . .	4
Total . . . . .	37

## D. General diseases.

14. Cirrhosis of the liver . . . . .	28
15. Nephritis . . . . .	22
16. Amyloid disease . . . . .	4
17. Morbus cordis . . . . .	14
18. Thrombosis of blood-vessels . . . . .	10
Total . . . . .	78

E. Other diseases . . . . . 8

F. Unknown causes . . . . . 14

The most striking facts detailed above are that malignant disease, tuberculous infections, cirrhosis of the liver, and nephritis are the commonest lesions found. To these must be added the changes present in the thoracic duct which, however, are always found secondarily to affections occurring elsewhere. Such a condition no doubt has, as a rule, a direct bearing on the causation of a milky ascites, but it must be admitted that there are several cases on record in which a thoracic duct has been obstructed by cancerous growth throughout its whole course without the appearance of a chylous effusion.

If we differentiate now between the chylous and pseudo-chylous cases it will be found that out of the 173 cases 71 are probably of a pseudo-chylous type. We say probably, because it is not always easy to come to a certain conclusion on some of the cases published owing to the incomplete character of the analysis carried out. Taking these, however, as being true pseudo-chylous effusions, an analysis of the morbid anatomy changes found gives the following results:—

*Pseudo-chylous effusions (71).*

## A. Tumours.

1. Carcinoma . . . . .	19 out of 57
2. Sarcoma . . . . .	8 " " 19
3. Lymphadenoma . . . . .	2 " " 4

## B. Infections.

4. Tuberculosis . . . . .	10 " " 33
5. Chronic peritonitis . . . . .	5 " " 9
6. Syphilis . . . . .	3 " " 3

## C. Affections of the thoracic duct and lymphatic system.

7. Obstruction of the thoracic duct . . . . .	1 " " 19
8. Compression and distension of lymphatics or chyle vessels . . . . .	2 " " 14

## D. General diseases.

9. Cirrhosis of the liver . . . . .	15 " " 28
10. Nephritis . . . . .	18 " " 22
11. Amyloid disease . . . . .	4 " " 4
12. Morbus cordis . . . . .	6 " " 14
13. Thrombosis of blood-vessels . . . . .	0 " " 10

E. Other diseases . . . . . 2 " " 8

F. Unknown causes . . . . . 6 " " 14

Here again malignant disease, tuberculosis, cirrhosis of the liver, and nephritis appear as the most frequent lesions. The affections of the thoracic duct are striking by their almost complete absence, as also are changes in the blood-vessels. It is interesting to note that the three cases of syphilis and the four occasions on which amyloid deposition had occurred are all found associated with a pseudo-chylous effusion.

As will be seen on reference to Synopsis A, a number of the cases of milky ascites were associated with effusions into one or both of the pleural cavities. These when milky were of the same type as that found in the peritoneal cavity; in many, however, the fluid present was of a simple serous character. The total number of milky pleural effusions found in 173 cases was 42, and of this number 18 were bilateral and 24 unilateral. Of serous effusions there were 17; unilateral 11 and 6 bilateral. There were in addition two examples of milky fluid in the pericardial sac and four of hydropericardium.

*Microscopical examination of milky effusions.* The results obtained by this method of procedure are only of value when combined with a chemical and physical investigation. The most important point has been to determine the presence or absence of free fat or of cells containing degeneration fat. That this fact when ascertained does give valuable information of the quantity of fat present is shown on chemical analysis. The average percentage of fat in milky fluids which do not show this body to be microscopically free is 0.2809, calculated on twenty-one samples in which the figures given may be considered reliable, while for thirty-eight samples which contained free fat the average figure is 1.2085 per cent. Unfortunately, the further analysis of these cases does not prove those with the lower fat content to be pseudo-chylous and vice versa. The most that can be said is that the absence of free fat is evidence in favour of a pseudo-chylous effusion, while the presence of free fat gives no information one way or the other unless a further examination is made. With regard to the cellular content which may be present, this, while of value for diagnostic purposes, has alone little use in helping to distinguish chylous from pseudo-chylous fluids.

### *Prognosis.*

Of the total number of cases tabulated, 173 in number, 116, or 67.8 per cent., are known to have died. Differentiating between chylous and pseudo-chylous the percentage mortality for the chylous cases is 66 per cent. and for the pseudo-chylous 70.4 per cent. The recoveries from chylous ascites number 15 (15 per cent.), while for the pseudo-chylous type of effusion the figure is 8.4 per cent., which shows that of the two the latter is of graver significance. It is interesting to note that of the 6 cases of pseudo-chylous ascites recovering, 4 were suffering from nephritis, and in the remaining 2 no diagnosis could be made. Of the chylous cases 15 recovered, 1 was suffering from chronic nephritis, 6 from chronic inflammatory conditions of the peritoneum, chiefly of a tuberculous

nature, 1 from morbus cordis with enlargement of the liver, and in the remaining 7 no diagnosis was made.

*Physical and Chemical Properties of Pseudo-chylous Ascites.*

Of all the fluids examined which are of the nature of pseudo-chylous effusions the colour was invariably pure white, or yellowish white, but the degree of turbidity various. Further, several observers have noted that the fluid removed at later tapplings is generally more opaque, and this was found to occur in all the fluids examined. The only exceptions appear to be those of Siredey (123), Gaucher (54), and Zypkin (156), where a milky fluid was later replaced by an ordinary ascitic fluid. The reverse condition of an ordinary ascites followed by a milky opalescent fluid was noted by Achard and Laubry (25) in one of their cases. The fluids when allowed to stand for a short time invariably show a creamy layer, the density of this layer depending upon the amount of fat present, and also upon the treatment of the fluid after removal from the body. Continuous shaking of the fluid, for example, completely modifies the condition of the substances which form the creamy layer; and subsequent storage in a cool place will not restore it. In all the fluids where this condition has been noted, the main bulk of the fluid has not lost its opalescence, and this clearly points to the fact that the milky appearance is not due to fatty materials. Besides the creaming of the fluid, a scanty white sediment is often found separating out, and this usually contains the cellular elements, a few fibrin-like coagula, and a finely granular debris, probably protein in nature. More rarely crystals of fatty acids, cholesterin, and phosphates are found in this sediment. Filtration through filter paper produces no alteration in the turbidity, and a similar result occurs with centrifugalization. Only in one of the cases (Fluid No. 3) did centrifugalization produce a clearing of the fluid, and this is not remarkable, when it is noted that the fluid itself tends to clear on standing. Filtration on the other hand through a Pasteur filter completely clears the fluids, and this was also observed by Apert (26) and Bernert (33). The residue on the porcelain candle is of a mucinoid character, and when extracted with water gives rise to an opalescent fluid similar to the original solution. The tendency to resist putrefaction, which is one of the most characteristic features of these effusions, seems to be bound up with the lecithin, since when this body is removed the fluids rapidly decompose. When chloroform is added as a preservative the fluids will keep for years without showing any signs of decomposition or putrefactive changes. Even without the addition of chloroform the sample will remain for a long time without any marked alteration in its homogeneity or its odour. Further, it seems that the larger the amount of lipine material present the longer will the fluid remain sterile. This relationship between lecithin and the resistance to putrefaction has already been referred to, and will be discussed later in its bearings on the resistance of other fluids to putrefactive changes. The microscopic examination of these fluids reveals the formed elements of blood, e.g. red blood corpuscles, polynuclear

and mononuclear leucocytes. The presence of the latter in excess is in favour of the effusion being lymphatic in origin. The occurrence of other more specialized cells is determined by the nature of the pathological condition, and whether these cells are degenerated or not. In inflammatory conditions we may find such cells containing granules which are not of the nature of fat, though produced by degeneration processes within the cell itself. A high cellular content is very unusual in these milky fluids. Besides cellular elements, many authors have noted the presence of fine refractile granules in active Brownian movement and described such an appearance as due to an emulsion of fat. They occur, however, in fluids with a very small quantity of fat, and furthermore do not react to stains such as osmic acid and Sudan III. These highly refractile particles appear to be of the nature of protein, and no doubt owe their optical properties to the associated lipine. They occurred in all the fluids which were examined, and in no case did they give any reactions for fat. The sediment in the second fluid described in the present paper when examined microscopically showed abundance of these fine granules, and this sediment contained the lecithin-globulin complex. A true pseudo-chylous fluid, therefore, is characterized by the presence of these minute granules, and the almost total absence of any microscopical fat globules. The specific gravity varies between 1.008 and 1.014, the average being about 1.010. The lowest figure recorded is that of Eisenschütz (49), 1.005; and the highest by Apert (26), 1.060 and 1.082. These latter figures may possibly be accounted for by the high protein content (9.7 per cent. and 6.6 per cent.) and that the fluid appears to resemble a purulent exudate. The reaction of the fluids is invariably alkaline, and very rarely neutral. Only in a case described by Mehu (84), and one by Rotmann (114), was the fluid acid, and in the latter this was undoubtedly due to bacterial contamination.

#### *Chemical Characters.*

*Proteins.* The fluids never coagulate spontaneously, showing the absence of fibrinogen and also their serous origin, and in very few cases did the fluid coagulate on heating. Heating, however, with acetic acid results in a dense coagulum and a clear supernatant fluid (Poljakoff (104)), Bernert (33), and Lambrior (71)). Treatment with alcohol has a similar effect (Zypkin (156)), as also half-saturation with  $(\text{NH}_4)_2\text{SO}_4$  (Joachim (194)), or full saturation (Taylor and Fawcett (137)). Ascoli (27), and later Joachim, showed that by dialysis a separation of the globulin took place with almost complete clearing of the solution. These observations have been confirmed above.

The removal of the opalescence in pseudo-chylous fluids by ether only occurred in two cases, one given by Variot (142) and the other by Leschischinski (75). Previous additions of caustic potash served to remove the opalescence in the case of Hirtz and Luys (62), and slightly in that of Zypkin. In one of the cases described in the present paper, viz. fluid No. 4, caustic potash

nature, 1 from morbus cordis with enlargement of the liver, and in the remaining 7 no diagnosis was made.

*Physical and Chemical Properties of Pseudo-chylous Ascites.*

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cluded that it was impossible to compare the two methods, and further that they did not differentiate two types of protein, since if the salt is added in small quantities at a time, and the results plotted in the form of a curve, no break in the continuity could be found. Burckhardt dialysed Hofmeister's protein fraction and found a large portion of it was soluble in water. This observation led up to the distinction between eu-globulin and pseudo-globulin, the latter being soluble in water, while the former is insoluble (Joachim and Freund (194).)

Now no one has shown so far any true distinction between the eu-globulin and pseudo-globulin of blood serum. One protein fraction of the blood certainly possesses the properties of the pseudo-globulin, but we hope definitely to establish that this is due to external factors, and not to the globulin itself. Joachim has demonstrated these two fractions in a milky fluid obtained from the abdominal cavity of a patient with cirrhosis of the liver. After dialysing the fluid for five days, he obtained a clear residual fluid and a copious precipitate. From this he concluded that the milky character of the fluid was due to a precipitable globulin. One-third saturation of the fluid with ammonium sulphate precipitated the eu-globulin fraction and the resulting filtrate did not differ in opalescence from the original fluid. On raising the strength of  $(\text{NH}_4)_2\text{SO}_4$  to half-saturation the pseudo-globulin was precipitated, and the fluid became quite clear. Therefore the pseudo-globulin fraction was the cause of the opalescence. Quantitatively the fluid contained 0.0331 gramme per cent. of eu-globulin and 0.245 gramme per cent. of pseudo-globulin. As a result of his experiments with dialysis he found that 53 per cent. of the eu-globulin fraction was insoluble in distilled water, and 27 per cent. of the pseudo-globulin fraction. The solubility of the eu-globulin fraction was normal according to the observations of Freund and Joachim, but the pseudo-globulin was very insoluble in distilled water. Furthermore, extraction of the dialysed residue with 0.6 per cent. solution of NaCl gave 0.0056 gramme per cent. of nitrogen, and subsequent treatment with a 1 per cent. solution of NaOH gave 0.0123 gramme per cent. of nitrogen. Joachim remarks that this observation is just the reverse to that when you treat serum globulin in the same way. Again, in his attempts to prove the presence of lecithin, he found the eu-globulin portion was quite free from phosphorus, whereas the pseudo-globulin portion gave a marked phosphorus reaction and contained 0.0360 gramme per cent. of lecithin in combination. He concluded that the lecithin was combined with the pseudo-globulin, and of the pseudo-globulin the portion which is insoluble in water gave rise to the turbidity of the fluid, i. e. 27 per cent. of the total.

Previous to the work of Joachim, Bernert had shown that lecithin was combined with the globulin in the pseudo-chylous fluids which he examined, and as such gave rise to the opalescent character of the fluids.

Wolff (153) in the same year as Bernert attributed the milky character of the pseudo-chylous effusion he examined to a cholesterol-ester combination with an eu-globulin. In this case the ratio of eu-globulin to pseudo-globulin had a much higher value than that given by Joachim. The eu-globulin which

was free amounted to 0.064, and that combined to 0.6661 gramme per cent., whilst the pseudo-globulin figure was 0.0208 gramme per cent.

In a private communication from Mr. W. B. Hardy of Cambridge he has informed us of some experiments which he has conducted on the serum proteins, and with his kind permission we quote them here. In separating the various fractions of serum by precipitation each fraction is found to hold in some close association cholesterol esters of fatty acids (palmitic, &c.). In view of the insolubility of these esters they must be present in the blood plasma in a very close association with the dissolved proteins, and when the ratio of ester to protein exceeds a certain definite amount then the solution of the protein is opalescent. In the various samples of pseudo-chylous fluids which we have had the opportunity of examining, the globulin fraction has always shown atypical properties. Only a very small quantity of the globulin was soluble in dilute saline solution, and this on analysis proved to be free from lipine material. The greater part of the globulin isolated was found to be quite insoluble, and gave an extremely dense milky fluid when shaken up with saline. This proved to contain lecithin in very close association with the globulin. Repeated attempts to isolate other lipines were without success, and only lecithin could be found in the fluids examined. When the lipine material is removed by long-continued extraction with warm ether, a white powder is obtained, which readily dissolves in dilute saline, and also in distilled water. This globulin therefore behaves in every way like the pseudo-globulin isolated by Joachim, but we do not propose to designate this fraction by that term. Having in view the above observations, and the considerable variations met with in the relative amounts of eu-globulin and pseudo-globulin so called, there seems no chemical basis for separating the globulin of serum into these two fractions. The solubility of the globulin, whether isolated from serum or from other sources, will no doubt depend on the nature and the amount of lipine material combined with it. In the observations of Hardy this point is brought out most strikingly, the globulin solution becoming opalescent when a certain stage of saturation with lipine is reached. This is the condition of the globulin in the milky effusions described by Joachim, Bernert, Wolff, Ceconi, and probably also those of Verdelli (144) and Aseoli. The same is true for the fluids obtained from the three cases above described. Additional support to this contention is given by Christen (191) in discussing the paper by Stryzowski (134). In a feebly turbid ascitic fluid with 3.06 grammes per cent. of protein he found 0.006 gramme of lecithin fixed to the globulin, and in another fluid of the same character with 4.56 per cent. of proteins 0.0028 gramme per cent. of lecithin was combined. However, in a strongly turbid ascitic fluid with a protein content of 6.9 per cent., 0.0168 gramme of lecithin was found associated with the globulin. A clear fluid from an ovarian cyst, on the other hand, showed the complete absence of any association of lecithin with globulin. Several observers have noted the presence of lecithin and also globulin in pseudo-chylous effusions, notably Michelli and Mattiolo, and others again, especially Achard (24), Achard and Laubry (25), Souques (129),

Poljakoff, and Zypkin, have stated that nucleo-albumin is present. The differentiation of these substances may easily mislead one, unless hydrolysis or fermentation is resorted to and the disintegration products carefully isolated. It therefore seems reasonable to suggest the general occurrence of this atypical globulin in all milky effusions where the opalescence is not due to fat, i. e. all pseudo-chylous effusions. The solubility of the globulin either in serum or in serous effusions is consequently conditioned by the amount of lipine material combined with it, and the latter will in addition influence the optical activity, the electrical charge on the colloidal particles in suspension, and also the relationship of globulin to electrolytes. Turning our attention to serum we find the proteins quite specialized, and this is not specific, but holds also for different animals (see analysis of Bunge and Abderhalden). The ratio of albumin to globulin is as 1.5:1, according to Hoppe-Seyler, but this is found to undergo considerable alteration under certain conditions. During starvation there is a larger amount of globulin present in the blood, and this was demonstrated in the following way by Morawitz (197). The volume of the blood in animals was reduced by bleeding, and then Locke's fluid (modified Ringer's solution) introduced. A rapid rise in the blood proteins occurred three hours after bleeding, and in two to four days they were entirely restored. During the period of this experiment the animals were kept without food. The most striking point noted was that the albumin fraction was restored more quickly than the globulin, although the latter was the last to disappear. These observations seem to have a very important bearing on the question under consideration, especially when the ratio of albumin to globulin shows wide variations. The question of the variations in the ratio of albumin to globulin with differences of sex may also be noted in passing.

Another feature of serum is that it will take up a considerable quantity of globulin without any alteration in its physical properties, i. e. it will filter readily, and is quite soluble. Attempts were made to produce an opalescent serum in this way, but provided the globulin is more or less free from lipines, only the addition of a large quantity will produce this effect. Judging from these observations it seems reasonable to assume that the proteins of serum under normal conditions are stable, and that the transport of transformed material derived from the intestine is carried out in some other way.

The ratio of albumin to globulin undergoes considerable alterations under pathological conditions. Bright noted that the serum was opalescent in some cases of albuminuria, and similar observations were made by Simon (182) (once in 4 cases), Rodier (three times in 15 cases), Castaigne (190), Widal and Siccard (201) (8 out of 13 cases), and Variot (142) (one case). The removal of large quantities of protein material from the blood, and more particularly the serum albumin, probably tends to increase the relative amount of serum globulin present. This in itself may give rise to an opalescent serum. As far as can be ascertained, the sera in all the cases mentioned above owed their opacity not to the contained fat, but to protein material, and especially was this



the case in Widal and Siccard's observations. The authors showed the presence of small refractile globules microscopically, and these were insoluble in ether, and unaffected by osmic acid. The blood serum, however, may be opalescent in scarlet fever, pneumonia, and rheumatic fever without any nephritis occurring. Fawcett and Boycott (192) have also published details of a case of sarcoma of the pancreas, where the blood plasma was creamy in appearance, and here again the opalescence was ascribed to a protein fraction, and not to fat or lecithin. A similar observation has been made by Rywosch (200). In diabetes the condition known as lipaemia is sometimes regarded as a serious symptom, and is generally attributed to fat. Wilson and Williams (202) found this condition in varying degree in the blood of fifteen cases of diabetes which they examined. Cholesterin and combined fatty acids were found to be present, and they attribute this condition to an abnormal fat metabolism. Roaf and B. Fischer have isolated a cholesterin ester from the opalescent serum in similar cases. These observations are quoted here as giving support to the probable cause of non-fatty opalescent sera and serous effusions. It is presumably to be found in the protein fractions, and further research will show whether the serum in these conditions contains a globulin-lipine combination. In only two of the recorded cases was an opalescent serum accompanied by a pseudo-chylous effusion, notably in the case of Achard, and in one case described by Variot. The occurrence of an opalescent serum is well known in animals after food has been taken, and Buchanan observed the same effect in man during digestion, but in these cases the presence of transformed fatty material may contribute largely to the production of the opacity. Seeing that in the case of serum under pathological conditions the stability of the proteins may undergo considerable alterations, it is not surprising to find the same variations in pseudo-chylous exudates. That the ratio of serum albumin to serum globulin varies within wide limits may be seen by reference to the chemical tables, that given by Bernert (Case 1) being as 1:14.5, and Verdelli 1:1. In general the percentage of serum albumin averages between 60-70 per cent. of the total proteins. In Joachim's case it amounted to 64.9 per cent., and in Wolf's case 75.7 per cent., a very high figure.

*Fats, lecithin, and cholesterin.* These substances represent the ether extract of pseudo-chylous fluids, and rarely do we find a total ether extract exceeding 1 gramme per cent. The fat content varies between 0.017 and 0.86 per cent., but in most cases it is more than 0.15 per cent. This latter figure, according to Letulle, represents the minimal quantity of fat which will give rise to a turbid fluid. The fat extracted from pseudo-chylous effusions consists largely of neutral fat, and this is usually yellowish in colour, and sets to a solid at room temperature. The melting-point of this fat ranges between 38°-40° C., and corresponds in every way to pathological fat. It presumably originates from the fatty degeneration of the cellular elements, and is in consequence unaffected by change in the diet. The quantity of fat present seems to depend on the length of stay in the abdominal cavity, and also upon the number of

previous tappings. As already noted, the fluid removed at later tappings is generally more yellowish in colour, and contains a larger quantity of fat.

The fat content of serum is generally lower than that for pseudo-chylous exudates, ranging, according to Englehardt, from 0.1 to 0.7 gramme per cent. Böningen found that even 0.85 per cent. could be present without in any way altering the general characters of the serum. Fawcett and Boycott in their case of pseudo-lipaemia found 0.38 gramme per cent. of fat, but the opalescence was shown not to be due to this substance. Jolles (195) in a clear peritoneal fluid found 0.280 gramme per cent. of fat. Finally, Verdelli, from an analysis of thirty serous fluids, whether exudates or transudates, concludes that neutral fat, fatty acids, and soaps, are present in all. Further, that the soaps are very much in excess of the fat, and in only one case was the quantity of soap exceeded by the fatty acids, lecithin, and cholesterin. In the three 'Chyliform' fluids which he examined a considerable quantity of fat was obtained.

In conclusion, it is obvious that the small quantity of fat contained in pseudo-chylous exudates plays little if any part in the production of the opalescence. It is present in the form of a very fine suspension, so that the obvious droplets are invisible under the microscope even when a  $\frac{1}{12}$ " objective is used. It does not give the ordinary reactions of fat when stained with osmic acid or Sudan III, and when extracted with ether or separated as a cream the opalescence of the fluid is almost unaltered.

Turning our attention to the lipine substances found in pseudo-chylous fluids, the two most constantly occurring are lecithin and cholesterin. The lecithin content of pseudo-chylous exudates varies between 0.003 and 0.274 gramme per cent. The highest figures recorded are for those of the cases described above, viz. 0.360 and 0.274 gramme per cent., and for one case of Michelli and Mattiolo 0.218 per cent. These higher figures are attributed to the introduction of improved methods of extraction and identification. The figures of other observers approximate very closely to 0.02 per cent., but Bernert and Ballmann (28) give a value of 0.096 per cent. The lecithin so obtained has proved to be a mono-amino mono-phosphatide, and to yield choline on hydrolysis, and is apparently of the mono-stearyl type. The presence of this substance is of interest, since to it many authors have attributed the milky appearance so characteristic of pseudo-chylous effusions (Strauss (132), Michelli and Mattiolo, Gross (56), and Mosse (90)). That lecithin itself is the only source of the milky-like character of these effusions has been contested by Poljakoff, and Christen (191). The arguments brought forward fell mainly under two heads, viz. the amount of lecithin required to render a solution milky, and the quantity of lecithin present in exudates and transudates. Mosse states that 0.008 gramme per cent. of lecithin will render distilled water milky, and consequently any figure above this will give rise to turbidity in a fluid. The turbidity, however, does not approximate that of pseudo-chylous effusions, since if an alcoholic solution of lecithin is added to water it produces an opalescence, but not so marked as the fluid from which the lecithin has been

extracted. Also in considering Mosse's statement the variations of solubility of lecithin in water and serum have to be taken into account. Michelli and Mattiolo further found that ether extraction did not clear the fluid, but if the lecithin was free and the cause of the opalescence it should have been removed by this treatment. With regard to the quantity of lecithin in various fluids, distinct variations are to be found. Christen found in a milky fluid 0.0077 gramme per cent. of lecithin, whereas in a clear ascitic fluid 0.316 gramme was present. Similarly, Jolles in a clear peritoneal fluid found 0.169 gramme per cent. In view of these facts lecithin by itself cannot play a very prominent part in the production of the opalescent character of pseudo-chylous ascites.

In the fluids examined by Bernert, Joachim, Christen, and the authors the contained lecithin was found to be almost entirely associated with the protein, and of the latter more especially the serum globulin. Joachim further stated that of the two globulin fractions the pseudo-globulin portion contained the lecithin. This association of a lipine with the globulin of the serum is a very stable one, and only with difficulty is the complex broken up into its constituent parts. Removal of this complex from a pseudo-chylous fluid either by dialysis, filtration through a Pasteur candle, precipitation, or exposure to radium rays results in a clear supernatant liquid. The opalescence of the fluids examined has been shown to be almost entirely due to this substance. In all probability many of the pseudo-chylous fluids previously examined were of the same nature, and this complex mistaken for a nucleo-protein to which it has a superficial resemblance. Achard and Laubry attributed the opalescence of their fluids to nucleo-protein, which dissolved in alkali and gave an opalescence similar to the original solution. In the fluids described by Souques, Poljakoff, and Zypkin nucleo-protein was stated to be present, and to be partly responsible for the milky character. Most of these observations were based on the phosphorus content only, and it is highly probable that in all these cases we are dealing with a substance similar to that described above. Further, the presence of lecithin has been demonstrated in many of these fluids. *Pseudo-chylous fluids, therefore, invariably contain lecithin, and it is highly probable that in most cases this exists mainly in combination with the globulin.* As a general rule the degree of turbidity is determined not by the amount of globulin present, but rather by the amount of lecithin which is in combination with it. This is well illustrated by reference to the figures quoted by Christen (*vide supra*), and also in the fluids which we have examined.

Fluid No. 1 derived from the first case was much more opalescent than fluid No. 2, and similarly the fluids from the second case were more opaque than those from the third case, this latter containing only a very small quantity of lecithin, being very faintly opalescent. The solubility coefficient of lecithin in water and serum respectively has been quite overlooked by many observers. Whereas a 0.008 per cent. solution of lecithin in distilled water is opalescent, much larger quantities can be taken up by serum without any alteration in its physical properties; in fact, as shown already, as much as 0.316 gramme per

cent. of lecithin may be present and the fluid still remain clear. The production of the opalescence, therefore, cannot be explained by the presence of lecithin alone, although normally lipines are very insoluble substances. When, however, they occur in association their solubility is considerably altered, and a corresponding alteration in the solubility of the complex results. This has already been demonstrated by Hardy (*vide supra*). *The opalescent character of milky fluids which are non-chylous is therefore due to a combination of the serum-globulin present with lipine material, the latter being usually in the form of lecithin.*

The production of the lecithin is possibly determined by the processes of degeneration of cellular material which takes place in the diseases where such an effusion results. In many respects it resembles the formation of pus, which is also characterized by the production of a large quantity of lecithin. In general pus fluids contain about 0.15 gramme per cent. of lecithin, but the amount varies with the degree of cellular destruction which has taken place. The pus cells themselves contain about 7.5 per cent. of lecithin and 7.2 per cent. of cholesterin. It seems highly probable that the destruction of the lecithin containing cell elements takes place in the blood itself, and that the lecithin so formed diffuses through the peritoneal membrane into the serous cavities. This would explain the sudden changes from a clear effusion to a milky one noted by some observers, or the reverse condition where a milky is later replaced by a clear transparent fluid.

The resistance to putrefaction so characteristic of all the milky fluids examined seems to be intimately bound up with the lecithin, as has already been pointed out, and this is very striking in view of the fact that lecithin readily undergoes autoxidation. When associated with protein it appears to be remarkably stable, but at the same time is able to exert its influence on the neutralization of toxines and bacterial growth. The chemical configuration of the lecithin molecule possibly accounts for this property, since it contains a larger number of hydroxyl groups capable of uniting with such bodies as ferments, proteins, sugar, and other lipines. The power of resisting putrefaction by micro-organisms, which has been conclusively shown to be due to lecithin, suggests a possible function of this body in the production of immunity. This subject is at present receiving attention with the object of ascertaining the part played by the lecithin in serum, bile, and other body fluids in resisting the attacks of micro-organisms.

The presence of cholesterin has not been demonstrated in any of the fluids described above, and in general this substance is only present in very small quantities in body fluids. Cholesterin is much more characteristic of cellular elements rather than of the fluids which surround them. Some observers have, however, noted the presence of this substance, notably: Mchu (0.0012 per cent.), Mosse (0.0078 per cent.), Wolff (0.056 per cent.), Hödlmoser (63) (0.06 per cent.), Souques (0.320 per cent.), Achard and Laubry (0.668 per cent.). Wolff further found that the cholesterin in the form of a cholesterin ester was exclusively

combined with the eu-globulin fraction, and as such was the cause of the opalescence. This observation is in accord with the observations made by Hardy previously mentioned in this paper.

*Carbohydrates.* The presence of sugar in milky effusions has received considerable attention owing to the dictum of Senator that all milky fluids containing sugar were chylous in origin. That this theory is now untenable has been fully demonstrated by subsequent workers. In the fluids described in this paper sugar was present only in one instance, though it was very carefully sought for. The behaviour of this sugar in the fluid under examination presents many interesting features, and has warranted a further investigation of all sugar containing body fluids. The facts ascertained, that the sugar did not pass through a Pasteur candle, and further was only partially dialysable, seem to be of great significance in ascertaining the condition of sugar in the blood and its mode of transport in the body. This subject is at present receiving attention. In view of the numerous discrepancies found in the literature it is difficult at the present juncture to give any definite values for the sugar content. Several observers have noted its presence to the extent of about 0.1 to 0.15 gramme per cent., whilst others have been unable to detect it, but this does not necessarily imply that it is absent in such effusions. Pascheles and Reichel (199) have demonstrated the presence of sugar in a variety of effusions, but the figures given rarely exceed 0.15 gramme per cent.

*Other organic substances.* The constituents of bile are rarely found in these fluids, as also urea and uric acid. When the latter occurs they approximate very closely the amounts found in ordinary serum. According to Naunyn and von Jacksch (198) uric acid should be present in all transudates.

*Inorganic constituents.* The most important constituents of the ash are the chlorides, which amount to between 0.5 and 0.7 per cent. Next in importance amongst the acid radicles are the phosphates, which show an almost constant value of 0.028 gramme per cent. This figure occurs independently of the amount of lecithin present. The amount of phosphoric acid present in milky effusions seems to be bound up with the abundance of added cellular material, which is strikingly small in these fluids.

The sulphur figure for chyle-like fluids presents rather an anomalous condition, since with a rise in protein there is no corresponding rise in sulphur content. This was at first thought to be due to the presence of some special substance rich in sulphur such as cystin, but careful search did not reveal any indications. Large quantities of the fluid were hydrolysed both by trypsin, and by acid, and the cystin isolated and weighed. The amount obtained corresponded very closely with the calculated value for the serum proteins isolated. The metabolism of the individual did not give any explanation of this discrepancy, although a diamine giving the reactions of putrescin was isolated from the urine obtained during the course of the treatment of the first case described above. In diseases of the lymphatic system a high  $\text{SO}_3$  content has been observed in the serum, and seems to be associated with an over-production

of lymphatic tissue. This may possibly account for the high figures in the fluid examined.

The value for the bases, particularly sodium and potassium, corresponds with those of serum, and the same is true for the oxides of calcium and magnesium. Finally, very small quantities of iron occur in all milky effusions, and this is possibly derived from the destruction of the cellular elements of the body, and from the iron taken in the food.

Summarizing the facts recorded above, it will be seen that the milky effusions (pseudo-chylous) are in reality modified serous effusions. The values found correspond very closely to those obtained for ordinary serous effusions, and a sharp line of distinction can be drawn between the milky effusions and true chyle. The importance of a complete chemical analysis of such an effusion cannot be over-estimated in making an exact determination of its nature, nor the value of these observations from the standpoint of the physician. Finally, the results supply additions to our knowledge of the chemistry of serum and the serum proteins.

#### *Physical and Chemical Properties of Chylous Ascites.*

The effusions containing chyle are generally white or yellowish-white in colour, and show a distinct creamy layer on standing. In contrast to pseudo-chylous effusions they possess a distinct odour, and this corresponds to the nature of the food ingested. Further, evidence of the presence of fibrinogen is shown by the appearance of a clot of fibrin after removal of the fluid from the body. Chylous effusions tend to accumulate very rapidly, and consequently large quantities are obtained at each paracentesis. It is worthy of note that the chylous fluid withdrawn at successive tapplings does not show any distinct variations either in the degree of turbidity or in its chemical composition. Under the microscope the presence of fat globules of various sizes which react to staining reagents is very characteristic, and apart from this the fluids have very few microscopic elements. The specific gravity in general exceeds 1.012, and may amount to as much as 1.023 (Stern (130)). The reaction of the fluids is generally alkaline, and only very occasionally neutral.

#### *Chemical Characters.*

The figures for the total solids show considerable variations, but a value below 4 per cent. is rarely found. The presence of fat in relatively large quantity accounts for the high figures, and consequently the proportion between the proteins and the total solids is low. The ash values are similarly influenced by the fat content, and, generally speaking, are very low when the figures for the total proteins are considered. The lowest ash figure recorded is

0.35 gramme per cent., and the highest value 1.022 per cent., but the average quantity of ash in chylous effusions amounts to approximately 0.8 per cent.

The protein constituents show very wide variations, the smallest figure being 1.2 per cent. (Landois (205)) and the highest figure 6.086. Of the various protein fractions serum albumin apparently occurs in the largest quantity, and serum globulin in little more than traces, in fact the protein fraction is largely composed of serum albumin, with the exception of small quantities of fibrin. Chylous effusions are free from nucleo-proteins, mucinoid substances, albumoses, and peptones. In no case hitherto recorded has a lecithin-globulin complex been isolated from a chylous effusion. With regard to the other extract of these fluids the greater part of it consists of fat. The figures for the fat range from 0.4 to 4.231 grammes per cent., but in most cases exceed 1 per cent. Its nature is determined by the fat contained in the food, and the quantity found in the fluid is also proportional to the amount ingested. In consequence, feeding experiments with various fats are of value in determining the nature of the effusion, especially if the melting-point of the fat in the diet is known. Not only do we find the melting-point of the fat present in chylous ascites different from the pathological fat present in certain pseudo-chylous effusions, but further, the acid figure, the saponification figure, and the ether figure are much lower than that for normal fat. In pathological fat there is also a greater free fatty acid content.

Turning now to the lipine substances, we find that whereas lecithin is characteristic of pseudo-chylous fluids the presence of cholesterin may be described as a feature of a chylous effusion. Lecithin has been noted by some observers to be present in only very small quantities, and by others to be absent from chylous ascites fluids. Cholesterin, on the other hand, appears to occur in appreciable quantities, and this is all the more striking since this substance is regarded rather as a cellular constituent than a constituent of the fluids of the body. The presence of sugar in chylous effusions has received special significance since the statement made by Senator that the presence of sugar was diagnostic of a chylous effusion. Sugar has been detected and estimated by several observers, the values ranging between 0.03 and 0.321 per cent. On the other hand, several observers have failed to find this substance in chylous fluids. The same remarks apply to pseudo-chylous effusions, and in consequence *the presence or absence of sugar is of no value in deciding whether a milky effusion is chylous or pseudo-chylous in nature.*

The inorganic salts in chylous effusions are in general present in smaller quantities than in pseudo-chylous ascites. The sulphates, however, occur in larger quantities, and this can be accounted for by the fact that the protein content is higher.

*Depression of freezing-point.* In close relationship to the inorganic salts in milky effusions we find corresponding variations in the amount of depression of the freezing-point. The difference between chylous and pseudo-chylous effusions is very marked, and at first sight appears a valuable method of

distinguishing the two types. The figures serve also to verify the statements already given as regards the serous origin of pseudo-chylous effusions and the relative quantity of salts in chylous and pseudo-chylous ascites. The cryoscopic determinations for pseudo-chylous ascites are  $-0.62^{\circ}\text{C}$ . (Mosse),  $-0.544^{\circ}\text{C}$ . (Vaquez and Esmonet) (141),  $-0.505$  and  $-0.48^{\circ}\text{C}$ . (Strzyzowski) (134),  $-0.59^{\circ}\text{C}$ .,  $-0.61^{\circ}\text{C}$ .,  $-0.56^{\circ}\text{C}$ ., and  $-0.60^{\circ}\text{C}$ . for the fluids described by the authors. Chylous ascitic fluids, on the other hand, show a value for the depression of the freezing-point of  $-0.593^{\circ}$  (Herczel) (60), whereas chyle from the thoracic duct according to Strauss is  $-0.51^{\circ}$ , and Bottazzi  $-0.615^{\circ}$ . The value for chyle, however, according to the latter author, may be as much as  $-0.640^{\circ}$ . For lymph we find figures such as  $-0.612^{\circ}$  and  $-0.623^{\circ}$ , and in blood serum the values ranging from  $-0.56^{\circ}$  (Achard and Laubry) to  $-0.595^{\circ}$  (Bottazzi, and also Abderhalden). In the case described by Vaquez and Esmonet a figure of  $-0.63^{\circ}$  for the blood serum was found, whereas the pseudo-chylous fluid gave a depression of  $-0.44^{\circ}$ . In conclusion, it will be seen that pseudo-chylous effusions approximate very closely ordinary blood serum as regards the values for the depression of the freezing-point, whereas chylous fluids correspond more closely to chyle.

If now we compare chylous and pseudo-chylous effusions we find the following are the most distinctive features of the two groups:—

#### *Chylous Ascites.*

1. Tends to accumulate very rapidly, and in consequence large volumes are removed at paracentesis.
2. Generally yellowish-white in colour and less perfectly emulsified.
3. Degree of opalescence more or less constant at successive tapplings.
4. Possesses an odour corresponding to the odour of the food ingested.
5. Microscopically the fluid contains fine fat globules but very few cellular elements.
6. Generally shows a distinct creamy layer on standing.
7. Specific gravity generally exceeds 1.012.
8. Depression of freezing-point about  $-0.51^{\circ}\text{C}$ ., and approximating that for chyle.
9. Total solids vary considerably, but usually greater than 4 %.
10. The total protein content generally exceeds 3 grammes per cent., and of this the serum-albumin is the largest fraction; globulin occurring only in traces.
11. Mucinoid substances absent.

#### *Pseudo-chylous Ascites.*

1. Collects more slowly, the volume of the fluid varying with the exciting pathological condition.
2. In colour a pure milky white solution in the form of an almost perfect emulsion.
3. The opacity generally increases or diminishes at successive tapplings.
4. Odourless.
5. Microscopically the quantity of free fat is variable; often numerous fine, highly refractile granules are present, and these do not give the reactions for fat. Cellular elements may be numerous and often contain fat; sometimes very scanty.
6. A cream may or may not form, but does not affect the opalescence; a sediment frequently settles out.
7. Specific gravity less than 1.012.
8. Depression of freezing-point ranges from  $-0.56^{\circ}$  to  $-0.61^{\circ}$ , and thus corresponds to the figures for blood serum.
9. Total solids rarely exceed 2 %.
10. The protein constituents vary between 1 and 3 grammes per cent., and of these the serum-globulin occurs in appreciable quantities.
11. Mucinoid sometimes present.



*Chylous Ascites.*

12. The fat content is generally high, varying from 0.4 to 4 %. The fat corresponds in all its properties to the fat contained in food.
13. Of the lipines, cholesterin is invariably found, and lecithin only occurs in traces.
14. No evidence of the presence of a lipine-globulin combination has been given by previous observers.
15. The salts and the organic substances present approximate to the values found for chyle obtained from the thoracic duct.

*Pseudo-chylous Ascites.*

12. The fat content is generally low, and may be present in traces only; in its melting-point and chemical composition it proves to be pathological fat.
13. The most characteristic lipine is lecithin, though cholesterin is occasionally present.
14. The lecithin is mainly combined with the globulin, and when present is the cause of the opalescence of the fluid. Such fluids resist putrefaction.
15. The salts and organic materials correspond closely to lymph and serous fluids.

The scheme of procedure necessary to establish whether a fluid obtained from a patient is chylous or pseudo-chylous in nature or a mixed form is as follows:—

The specific gravity, total solids, and ash should be ascertained as soon as possible after withdrawal. The fat and lipines may be removed in several ways, either by ether extraction of the fluid, or extraction with hot alcohol. The ordinary method of extraction with ether has, however, many disadvantages, chief amongst them being the fact that the proteins present are partially precipitated, and in pseudo-chylous effusions the lecithin as well. By precipitating the proteins with boiling alcohol, and repeated extraction of the residue with alcohol, the lipines and fat are entirely removed. The alcohol residue can then be extracted with ether, and the fat and other ether-soluble substances isolated. The nature of the fat, its melting-point, saponification figure, and ether figure should be observed, as by this means a distinction between normal human fat and pathological fat can be made. The presence of lecithin and its condition in the fluid is also of importance, and this can be established either by precipitation methods or by dialysis. The presence or absence of sugar appears to be of little value for diagnostic purposes, since it may or may not be present in either of the two types of effusion. The other organic constituents, such as urea, uric acid, bile components, occur in very small quantities and are apparently of no special significance. The presence of such inorganic salts as chlorides and phosphates may be ascertained by an analysis of the ash. Finally, the depression of the freezing-point may be determined, and this gives an indication of the quantity and distribution of the inorganic

*Conclusions.*

1. The conclusions arrived at are confirmed as a result of the analysis of the fluid obtained from the patient with chylous ascites.
2. That two main types of ascites are present, namely, chylous and pseudo-chylous.

3. That the occurrence of a milky ascites is characteristic of no specific morbid anatomy lesion.
4. That the prognosis in milky ascites is grave.
5. That the mortality in pseudo-chylous ascites is higher (70.4 per cent.) than in chylous ascites (66 per cent.).
6. That a complete chemical and physical examination is necessary to differentiate with certainty the two types of milky ascites.
7. That the results obtained have a direct bearing on the question of the chemical physiology of the blood serum, particularly with regard to the serum-proteins and carbohydrates present.

#### A. SYNOPSIS OF THE RECORDED CASES OF CHYLOUS AND PSEUDO-CHYLOUS ASCITES.

- Case 1 (Stevenson, 1860). Remarks: Durham's case; milky fluid; chylous.
- Case 2 (Stevenson, 1860). Remarks: Moxon's case; milky fluid; pseudo-chylous.
- Case 3 (Oppolzer, 1861). Age 42. Sex M. Disease: Cirrhosis of liver (atrophic), morbus cordis, thrombosis of subclavian veins. Result: Death. Remarks: Tapped 3 times; milky fluid; microscopically no free fat; thoracic duct blocked by clot, walls thickened.
- Case 4 (Rokitansky, 1865). Age 62. Sex F. Disease: Morbus cordis. Result: Death. Remarks: Autopsy; milky fluid; dilatation of chyle vessels and receptaculum chyli, walls thickened; thoracic duct obstructed and dilated; bilateral chylothorax.
- Case 5 (Cayley, 1866). Age 16. Sex M. Disease: Lymphosarcoma. Result: Death. Remarks: Autopsy; turbid yellow fluid; microscopically lymphocytes and endothelial cells; thoracic duct obstructed and dilated throughout; perforation of receptaculum chyli on anterior surface.
- Case 6 (Lücke and Klebs, 1867). Age 43. Sex F. Disease: Carcinoma of pancreas. Result: Death. Remarks: Autopsy; 14 litres; milky fluid.
- Case 7 (Wilks and Ormerod, 1868). Age 24. Sex M. Disease: ? Lymphadenoma, ? Sarcoma, thrombosis of left subclavian vein. Result: Death. Remarks: Tapped 6 times; 76 pints; milky fluid; microscopically no free fat; granular cells and refractile granules present; thoracic duct normal; left hydrothorax.
- Case 8 (Klebs, 1869). Age 10. Disease: Fatty degeneration of peritoneum. Result: Death. Remarks: Tapped many times.
- Case 9 (Bergeret, 1873). Age 27. Sex F. Disease: Tuberculosis, pulmonary and peritoneal. Result: Death. Remarks: Tapped twice; milky turbid fluid; microscopically free fat, no cells; no autopsy.
- Case 10 (Munson, 1873). Sex F. Disease: Embolism of pulmonary artery. Result: Death. Remarks: Autopsy; milky fluid; thoracic duct perforated in neighbourhood of pancreas by rupture.
- Case 11 (Wilhelms, 1874). Age  $\frac{1}{2}$ . Disease: Abdominal tumour in region of spine. Result: Death. Remarks: Tapped 10 times; milky fluid; thoracic duct ruptured by coughing.
- Case 12 (Friedrich, 1875). Age 12. Sex F. Disease: General tuberculosis, tuberculous peritonitis. Result: Death. Remarks: Tapped 5 times; 8 litres; milky fluid; 'hydrops adiposus'; microscopically free fat and degenerated cells containing fat.
- Case 13 (Quincke, 1875). Age 50. Sex M. Disease: Injury to abdomen, fractured ribs, 7-9 left side. Result: Death. Remarks: Autopsy; 150 c.c. fluid; milky; right chylothorax; left hydrothorax; chyle vessels of mesentery and intestinal mucosa not injected.
- Case 14 (Quincke, 1875). Age 30. Sex F. Disease: Trauma. Result: Death.

**Remarks:** Tapped 6 times; first tapping, 10 litres; milky fluid; microscopically free fat; autopsy; no evidence of injury to thoracic duct or chyle vessels.

Case 15 (Quinke, 1875). Age 33. Sex F. Disease: Carcinoma of peritoneum. Result: Death. **Remarks:** Tapped; milky fluid; 'hydrops adiposus'; microscopically free fat.

Case 16 (Quinke, 1875). Age 10. Sex F. Disease: ? Tuberculous peritonitis. **Remarks:** Tapped; 5 litres; milky fluid; 'hydrops adiposus'; microscopically free fat.

Case 17 (Pelletier, 1875). Age 24. Sex F. Result: Recovered. **Remarks:** Tapped; milky fluid; chylothorax.

Case 18 (Sydney Jones, 1875). Age 31. Sex M. Disease: Lymphangioma of leg. **Remarks:** Tapped 3 times; milky fluid; microscopically, lymphocytes, red cells, fine granules.

Case 19 (Ballmann, 1876). Age 39. Sex F. Disease: Tuberculous peritonitis. Result: Death. **Remarks:** Tapped once; 8.53 litres; milky fluid; microscopically, small granules, no cells, no free fat; thoracic duct not obstructed.

Case 20 (Mehu, 1877). Disease: Cirrhosis of liver. **Remarks:** Milky fluid.

Case 21 (Mehu, 1877). Disease: Albuminuria. **Remarks:** Milky fluid.

Case 22 (Stern, 1880). Age: boy. Disease: No diagnosis. Result: ? Recovered. **Remarks:** Tapped.

Case 23 (Smidt Guttman, 1881). Age 11. Sex M. Disease: Chronic peritonitis. Result: Death. **Remarks:** Tapped once; 6.35 litres; milky fluid; autopsy; 2.0 litres; milky fluid; microscopically free fat; thoracic duct and chyle vessels normal.

Case 24 (Brieger, 1881). Age 44. Sex F. Disease: Carcinoma of stomach; metastases in mesentery and liver. Result: Death. **Remarks:** Tapped 3 times; 17 litres; milky fluid; microscopically free fat, many cells containing fat; thoracic duct not affected.

Case 25 (Brieger, 1881). Age 50. Sex F. Disease: Carcinoma of stomach; metastases in mesentery and liver. Result: Death. **Remarks:** Tapped twice; 19 litres; milky fluid; autopsy, 4 litres; microscopically free fat, no cells; thoracic duct not affected.

Case 26 (Veil, 1882). Age 25. Sex F. Disease: Liver cirrhosis. Result: Death. **Remarks:** Milky fluid.

Case 27 (Gaucher, cited by Veil, 1882). Age 47. Sex M. Disease: Cirrhosis of liver. Result: Death. **Remarks:** Milky fluid; microscopically free fat.

Case 28 (Gaucher, cited by Veil, 1882). Age 39. Sex M. Disease: Cirrhosis of liver. Result: Death. **Remarks:** Tapped twice, ordinary ascitic fluid; later tapplings, milky fluid; microscopically free fat.

Case 29 (Gaucher, cited by Veil, 1882). Age 11. Disease: Sarcoma of omentum and mesentery. Result: Death. **Remarks:** Milky fluid; thoracic duct normal.

Case 30 (Enzmann, 1883). Age 60. Sex F. Disease: Carcinoma of uterus. Result: Death. **Remarks:** Autopsy; 30 c.c.; dark yellow fluid; thoracic duct carcinomatous at origin and irregularly dilated; bilateral hydrothorax.

Case 31 (Recklinghausen, 1883). Result: Death.

Case 32 (Letulle, 1884). Age 8. Sex M. Disease: Morbus cordis. Result: Death. **Remarks:** Tapped once; 2.0 litres; milky fluid; microscopically free fat; bilateral hydrothorax; no autopsy.

Case 33 (Whitla, 1885). Age 13. Sex M. Disease: Miliary tuberculosis. Result: Death. **Remarks:** Tapped 6 times; 72 litres; milky fluid; microscopically no free fat; cellular elements present, and finely granular material; receptaculum chyli dilated, with small perforation at lower end.

Case 34 (Senator, 1885). Sex F. Disease: Carcinoma of ovary, metastases in peritoneum. Result: Death. **Remarks:** Milky fluid; 'hydrops adiposus'.

Case 35 (Letulle, 1885). Age 2 $\frac{1}{2}$ . Sex M. Disease: No diagnosis made. Result: Recovered. **Remarks:** Tapped 4 times; 13 litres; milky fluid.

Case 36 (Schaller, 1886). Age 10. Sex M. Disease: Lympho-sarcoma of retroperitoneal glands. Result: Death. **Remarks:** Autopsy; milky yellow fluid; thoracic duct involved at its origin.

Case 37 (Strauss, 1886). Age 61. Sex M. Disease: Carcinoma of pylorus, generalized peritoneal metastases; rupture of chyle vessel in mesentery. Result: Death. **Remarks:** Tapped 3 times; 12 litres; milky fluid contains fine fat granules; thoracic duct not obstructed.

Case 38 (Duffey, 1886). Age 52. Sex F. Disease: Chronic tuberculosis. Result: Death. Remarks: Tapped 3 times; milky fluid; contains no free fat, microscopically; large granular cells.

Case 39 (Murphy, 1886). Age 19. Sex F. Disease: ?Trauma. Result: Recovered. Remarks: Laparotomy; milky fluid.

Case 40 (Minkowski, 1886). Age 56. Sex M. Result: Recovered. Remarks: Tapped 5 times; 27.8 litres; milky fluid.

Case 41 (Rabinowitz, 1887). Age 45. Sex F. Disease: Miliary tuberculosis of peritoneum and pleura. Result: Death. Remarks: Tapped 3 times; 10 litres; turbid yellow fluid; microscopically free fat.

Case 42 (Rabinowitz, 1887). Age 59. Sex F. Disease: Carcinoma of gall-bladder, metastases in mesentery. Result: Death. Remarks: Tapped once; turbid milky fluid; contains free fat; cellular elements contain fat; compression and distension of lymphatics.

Case 43 (Sécretan, 1887). Age 58. Sex F. Disease: Tuberculous peritonitis, chronic nephritis. Result: Death. Remarks: Tapped 4 times; 30 litres; milky fluid; contains free fat.

Case 44 (Terillon, 1888). Age 35. Sex F. Disease: No diagnosis. Result: Recovered. Remarks: Tapped twice and laparotomy; 22.5 litres; milky brown fluid, consisting of a fine emulsion of free fat; peritoneum injected; lymphatics normal.

Case 45 (Hirschler and Buday, 1889). Age 31. Sex M. Disease: Generalized carcinomatosis of peritoneum. Remarks: Tapped twice; 14.5 litres; milky fluid; contains free fat.

Case 46 (Haswell, 1889). Age 26. Sex M. Disease: Sarcoma of pelvis, metastases in abdominal glands and lungs. Result: Death. Remarks: Tapped 6 times; 568 oz.; autopsy, large quantity of fluid; does not contain free fat, but granular cells; thoracic duct involved in growth.

Case 47 (Smith (quoted by Busey), 1889). Age 9. Sex M. Disease: No diagnosis. Remarks: Tapped once; 28 pints; milky fluid; contains lymph cells and a few red cells.

Case 48 (Newcomb, 1890). Age 2. Sex M. Disease: No diagnosis. Result: Recovered. Remarks: Tapped twice; 2.5 litres; milky white fluid; no free fat; granular cells.

Case 49 (Renvers, 1890). Age 36. Sex F. Disease: Cirrhosis of liver, facial erysipelas, thrombosis of veins at superior thoracic opening, purulent peritonitis. Result: Death. Remarks: Tapped; milky fluid; contains free fat and leucocytes; bilateral hydrothorax; thoracic duct dilated and tortuous and obstructed at entrance to veins.

Case 50 (Curwen (Fenwick), 1890; Smith, 1891). Age 67. Sex F. Disease: Miliary carcinoma of peritoneum. Result: Death. Remarks: Tapped 4 times; 17.5 litres; milky fluid (at the autopsy fluid was clear); contains free fat; thoracic duct normal; perihepatitis; right hydrothorax.

Case 51 (Reichenbach, 1891). Age 58. Sex M. Disease: Lympho-sarcoma. Result: Death. Remarks: Tapped 3 times; 17.75 litres; milky fluid; contains free fat, moderate cellular content. Right chylothorax.

Case 52 (Zawadzky, 1891). Age 67. Sex F. Disease: Carcinoma of stomach, generalized carcinomatosis of peritoneum. Result: Death. Remarks: Tapped 3 times; milky fluid; thrombosis of innominate and left subclavian vein; chylothorax.

Case 53 (Martin, 1891). Age 39. Sex F. Disease: Thrombosis of left subclavian vein. Result: Death. Remarks: Tapped twice; 7.3 litres; milky yellow fluid; contains free fat, and a few leucocytes; intestinal lymphatics dilated and containing milky fluid; chylothorax.

Case 54 (Nieuwondt and Rozenzweig, 1892). Age 1 $\frac{3}{4}$ . Sex F. Disease: Chronic peritonitis, ? tuberculous. Result: Recovered. Remarks: Tapped 11 times; 19.32 litres; milky fluid containing free fat.

Case 55 (Pounds, 1892). Age 10. Sex F. Disease: Tuberculous peritonitis. Result: Recovered. Remarks: Laparotomy; 4.5 litres; milky fluid.

Case 56 (Vali, 1892). Age 30. Sex F. ? Cirrhosis of liver, ? malignant disease of abdomen. Remarks: Tapped many times; milky white fluid; contains free fat, lymph cells, and red cells.

Case 57 (Lion, 1893). Age 57. Sex F. Disease: Carcinoma of left ovary. Result:

Remarks: Tapped 6 times; first tapping, 10 litres; milky fluid; microscopically free fat; autopsy; no evidence of injury to thoracic duct or chyle vessels.

Case 15 (Quinke, 1875). Age 33. Sex F. Disease: Carcinoma of peritoneum. Result: Death. Remarks: Tapped; milky fluid; 'hydrops adiposus'; microscopically free fat.

Case 16 (Quinke, 1875). Age 10. Sex F. Disease: ?Tuberculous peritonitis. Remarks: Tapped; 5 litres; milky fluid; 'hydrops adiposus'; microscopically free fat.

Case 17 (Pelletier, 1875). Age 24. Sex F. Result: Recovered. Remarks: Tapped; milky fluid; chylothorax.

Case 18 (Sydney Jones, 1875). Age 31. Sex M. Disease: Lymphangioma of leg. Remarks: Tapped 3 times; milky fluid; microscopically, lymphocytes, red cells, fine granules.

Case 19 (Ballmann, 1876). Age 39. Sex F. Disease: Tuberculous peritonitis. Result: Death. Remarks: Tapped once; 8.53 litres; milky fluid; microscopically, small granules, no cells, no free fat; thoracic duct not obstructed.

Case 20 (Mehu, 1877). Disease: Cirrhosis of liver. Remarks: Milky fluid.

Case 21 (Mehu, 1877). Disease: Albuminuria. Remarks: Milky fluid.

Case 22 (Stern, 1880). Age: boy. Disease: No diagnosis. Result: ?Recovered. Remarks: Tapped.

Case 23 (Smidt Guttman, 1881). Age 11. Sex M. Disease: Chronic peritonitis. Result: Death. Remarks: Tapped once; 6.35 litres; milky fluid; autopsy; 2.0 litres; milky fluid; microscopically free fat; thoracic duct and chyle vessels normal.

Case 24 (Brieger, 1881). Age 44. Sex F. Disease: Carcinoma of stomach; metastases in mesentery and liver. Result: Death. Remarks: Tapped 3 times; 17 litres; milky fluid; microscopically free fat, many cells containing fat; thoracic duct not affected.

Case 25 (Brieger, 1881). Age 50. Sex F. Disease: Carcinoma of stomach; metastases in mesentery and liver. Result: Death. Remarks: Tapped twice; 19 litres; milky fluid; autopsy, 4 litres; microscopically free fat, no cells; thoracic duct not affected.

Case 26 (Veil, 1882). Age 25. Sex F. Disease: Liver cirrhosis. Result: Death. Remarks: Milky fluid.

Case 27 (Gaucher, cited by Veil, 1882). Age 47. Sex M. Disease: Cirrhosis of liver. Result: Death. Remarks: Milky fluid; microscopically free fat.

Case 28 (Gaucher, cited by Veil, 1882). Age 39. Sex M. Disease: Cirrhosis of liver. Result: Death. Remarks: Tapped twice, ordinary ascitic fluid; later tapplings, milky fluid; microscopically free fat.

Case 29 (Gaucher, cited by Veil, 1882). Age 11. Disease: Sarcoma of omentum and mesentery. Result: Death. Remarks: Milky fluid; thoracic duct normal.

Case 30 (Enzmann, 1883). Age 60. Sex F. Disease: Carcinoma of uterus. Result: Death. Remarks: Autopsy; 30 c.c.; dark yellow fluid; thoracic duct carcinomatous at origin and irregularly dilated; bilateral hydrothorax.

Case 31 (Recklinghausen, 1883). Result: Death.

Case 32 (Letulle, 1884). Age 8. Sex M. Disease: Morbus cordis. Result: Death. Remarks: Tapped once; 2.0 litres; milky fluid; microscopically free fat; bilateral hydrothorax; no autopsy.

Case 33 (Whitla, 1885). Age 13. Sex M. Disease: Miliary tuberculosis. Result: Death. Remarks: Tapped 6 times; 72 litres; milky fluid; microscopically no free fat; cellular elements present, and finely granular material; receptaculum chyli dilated, with small perforation at lower end.

Case 34 (Senator, 1885). Sex F. Disease: Carcinoma of ovary, metastases in peritoneum. Result: Death. Remarks: Milky fluid; 'hydrops adiposus'.

Case 35 (Letulle, 1885). Age 2 $\frac{1}{2}$ . Sex M. Disease: No diagnosis made. Result: Recovered. Remarks: Tapped 4 times; 13 litres; milky fluid.

Case 36 (Schaller, 1886). Age 10. Sex M. Disease: Lympho-sarcoma of retroperitoneal glands. Result: Death. Remarks: Autopsy; milky yellow fluid; thoracic duct involved at its origin.

Case 37 (Strauss, 1886). Age 61. Sex M. Disease: Carcinoma of pylorus, generalized peritoneal metastases; rupture of chyle vessel in mesentery. Result: Death. Remarks: Tapped 3 times; 12 litres; milky fluid contains fine fat granules; thoracic duct not obstructed.

Case 77 (Corselli and Frisco, 1896). Age 40. Sex F. Lympho-sarcoma of retroperitoneal glands. Result: Death. Remarks: Tapped once; large quantity of milky fluid; cells of varying size in fluid; no autopsy allowed.

Case 78 (Corselli and Frisco, 1896). Age 40. Sex M. Disease: Sarcoma of retroperitoneal glands, metastases in liver. Result: Death. Remarks: Tapped once; 9 litres; autopsy, 4 litres; no metastases in thorax; same characters as preceding.

Case 79 (Corselli and Frisco, 1896). Age 30. Sex F. Disease: Growth in abdomen in umbilical region. Remarks: Tapped once; turbid milky fluid, microscopically and chemically same as two previous cases.

Case 80 (Merklen, 1897). Age 61. Sex F. Disease: Cirrhosis of liver (atrophic) (traumatic injury to lacteals). Result: Death. Remarks: Tapped once; 11 litres; milky fluid; free fat, leucocytes and endothelial cells; left chylothorax.

Case 81 (Soupault, 1897). Age 40. Sex F. Disease: Carcinoma of caecum. Remarks: Tapped once; milky fluid; contained many mononuclear cells filled with refractile granules; polynuclear cells.

Case 82 (Bayer, 1897). Age 19. Sex M. Disease: Tuberculous peritonitis. Result: Recovered. Remarks: Tapped twice; 12-35 litres; milky fluid, contained free fat; chylous fluid.

Case 83 (Rotmann, 1897). Age 42. Sex M. Disease: Carcinoma of stomach, metastases in peritoneum and mesenteric glands. Result: Death. Remarks: Tapped twice; 9-6 litres; milky fluid; free fat; thoracic duct compressed at origin by growth; chyle vessels dilated.

Case 84 (Rotmann, 1897). Age 59. Sex M. Disease: Carcinoma of stomach, metastases in liver. Result: Death. Remarks: 400 c.c. of turbid yellow fluid obtained at necropsy; free fat; fatty degeneration of peritoneum.

Case 85 (Sarrazin, 1897). Sex F. Disease: Cysto-carcinoma of ovary, metastasis in mesenteric glands. Result: Death. Remarks: Tapped many times; about 62 litres; richly cellular milky fluid; chyle vessels of mesentery varicose and dilated; thoracic duct obstructed at origin by secondary deposit; permeable in thorax but not in abdomen; chylothorax.

Case 86 (Mackie Whyte, 1897). Age 21. Sex F. Disease: Morbus cordis, ? tuberculosis, ? obstruction of thoracic duct in neck by tuberculous glands. Result: Death. Remarks: Tapped once; 4-348 litres; milky fluid; no free fat; bilateral chylothorax and chylo-pericardium; no post-mortem.

Case 87 (Hirtz and Luys, 1897). Age 57. Sex F. Disease: Carcinoma of stomach, metastases in mesentery, pancreas and prevertebral glands. Result: Death. Remarks: Tapped once; 8-5 litres, and 9 litres at necropsy; free fat; thoracic duct embedded in growth.

Case 88 (Rendu, given in 1897, discussing Hirtz and Luys's case). Sex F. Disease: Morbus cordis, enlarged liver. Result: Recovered. Remarks: Tapped 4 times, ordinary ascites; next two tapplings, milky fluid; later tapplings, ordinary ascites; R. suggests rupture of thoracic duct as cause of the milky ascites.

Case 89 (Ceconi, 1897). Age 41. Sex M. Disease: Ascites and pleurisy, ? origin. Result: Death. Remarks: Tapped twice; 14 litres.

Case 90 (Ringer, 1897). Age 46. Sex M. Disease: Lymphadenoma, albuminuria. Result: Death. Remarks: Tapped once; 3-5 litres; milky fluid which clotted; free fat; thoracic duct compressed in chest. (Described by Batty Shaw.)

Case 91 (Apert, 1897). Age 43. Sex M. Disease: Morbus cordis, plumbism, peri-hepatitis. Result: Death. Remarks: Tapped 20 times, from May to October, 1896; Oct. 20 milky fluid and subsequently every 12 days up to February, 1897, when he died; 10-15 litres of milky fluid removed each time; free fat; thoracic duct not obstructed.

Case 92 (Day, 1897). Age 54. Sex M. Result: Recovered. Remarks: Tapped many times from 1895 to 1897; 555 litres; free fat.

Case 93 (Hödlmoser, 1898). Age 59. Sex M. Disease: Morbus cordis. Result: Recovered. Remarks: Tapped once; 5-8 litres; free fat; no cellular elements.

Case 94 (Czerny, 1898). Age 18. Sex F. Disease: Angio-sarcoma of ovary. Remarks: Tapped once; 4-5 litres; milky fluid; free fat.

Case 95 (Ceconi, 1899). Age 46. Sex M. Disease: Cirrhosis of liver, chronic peritonitis. Result: Death. Remarks: Tapped 7 times; 37 litres; milky fluid; free fat; lymphocytes;

endothelial cells; polynuclear cells containing fat; autopsy, 1 litre clear fluid; thoracic duct not obstructed.

Case 96 (Ceconi, 1898). Age 49. Sex M. Similar case in all particulars to No. 95.

Case 97 (Eshner, 1899). Age 25. Sex M. Disease: Acute tuberculosis. Result: Death. Remarks: 150 c.c. milky fluid found in pelvis at necropsy.

Case 98 (Talma, 1900). Age 67. Disease: Cirrhosis of liver, chronic peritonitis. Result: Death. Remarks: Tapped; milky fluid; 'Talma' operation; no necropsy; milkiness said to be due to Hammarsten's mucoid substance.

Case 99 (Schterbatscheff, 1900). Sex M. Disease: Syphilis, renal symptoms. Result: Death. Remarks: Milky fluid obtained at post mortem; no free fat.

Case 100 (Vidal and Merklen, 1900). Age 50. Sex M. Disease: Hypertrophic cirrhosis of liver, tuberculosis of lungs. Result: Death. Remarks: Tapped twice; 12.5 litres; milky fluid; no free fat; lymphocytes 100,000 per c.mm., and leucocytes; no fatty degeneration in cells; blood serum not opalescent; thoracic duct not obstructed.

Case 101 (Vaquez and Esmonet, 1900). Age 63. Sex M. Disease: Malignant disease of abdomen. Remarks: Tapped 4 times; 25 litres; milky fluid; free fat leucocytes and red cells.

Case 102 (Siredey, given in discussing the previous case, 1900). Age 60. Sex M. Disease: Cirrhosis of liver. Result: Death. Remarks: Tapped 5 times; milky fluid; first two tappings 29 litres of milky fluid; next three progressively less milky; sixth tapping 13 litres of serous citron fluid.

Case 103 (Variot, 1900). Age 4. Sex F. Disease: Chronic nephritis (post diphtheritic), anasarca, coma. Result: Recovered. Remarks: Tapped 3 litres milky fluid when unconscious; recovered consciousness directly after tapping.

Case 104 (Variot, 1900). Age 11. Sex M. Disease: Chronic nephritis, anasarca. Remarks: Tapped; milky fluid; free fat; blood serum opalescent; urine opalescent and contained 0.02% of fat; boy on milk diet.

Case 105 (Michelli and Mattiolo, 1900). Age 60. Sex M. Disease: Cirrhosis of liver, chronic peritonitis. Result: Death. Remarks: Tapped; milky yellow fluid; free fat; bilateral chylothorax.

Case 106 (Michelli and Mattiolo, 1900). Age 20. Sex M. Disease: Carcinoma of pancreas, metastases in peritoneum and liver. Result: Death. Remarks: Tapped; 10.5 litres milky fluid; free fat, leucocytes, and endothelial cells.

Case 107 (Michelli and Mattiolo, 1900). Age 27. Sex M. Disease: Sarcoma of spleen, secondary to growth in abdominal glands. Result: Death. Remarks: Tapped; milky yellowish fluid; no free fat.

Case 108 (Michelli and Mattiolo, 1900). Age 19. Sex M. Disease: Adhesive pericarditis. Result: Death. Remarks: Tapped; milky fluid, contains finely granular material, leucocytes, endothelial cells; thoracic duct normal.

Case 109 (Michelli and Mattiolo, 1900). Disease: Cirrhosis of liver. Result: Death. Remarks: Milky yellow fluid; no free fat, but leucocytes and endothelial cells.

Case 110 (Michelli and Mattiolo, 1900). Disease: Cirrhosis of liver. Remarks: Same as preceding fluid.

Case 111 (Michelli and Mattiolo, 1900). Disease: Tuberculous peritonitis, tuberculosis of apex of right lung. Remarks: Fluid same as preceding.

Case 112 (Michelli and Mattiolo, 1900). Disease: Cirrhosis of liver. Remarks: Fluid same as preceding.

Case 113 (Michelli and Mattiolo, 1900). Disease: Tuberculous peritonitis. Remarks: Fluid same as preceding.

Case 114 (Michelli and Mattiolo, 1900). Disease: Calcified pericardium. Result: Death. Remarks: Fluid same as preceding.

Case 115 (Michelli and Mattiolo, 1900). Remarks: Endothelial cells containing fat, otherwise fluid same as preceding; bilateral chylothorax.

Case 116 (Ascoli, 1900). Disease: Tuberculous peritonitis, tuberculosis of lungs and pleura. Remarks: Milky yellowish fluid; no free fat, but leucocytes and endothelial cells.

Case 117 (Gross, 1900). Age 40. Sex M. Disease: Carcinoma of stomach. Result: Death. Remarks: Tapped twice; milky fluid; no free fat, but leucocytes and red cells.

Case 118 (Poljakoff, 1900). Age 48. Sex F. Disease: Syphilitic disease of liver, nephritis. Result: Recovered. Remarks: Tapped; 9 litres; milky fluid; no free fat, but leucocytes and endothelial cells, and fine granules.

Case 119 (Halliday Croom, 1900). Age 39. Sex F. Disease: Cancer of pylorus, metastases in mesentery and miliary deposits on small intestine. Result: Death. Remarks: Tapped twice; 20-74 litres; milky fluid; contains finely emulsified fat and granular debris; thoracic duct obstructed by external pressure at origin.

Case 120 (Kahn, 1900). Age 66. Sex F. Disease: Carcinoma of stomach, generalized peritoneal carcinomatosis, metastases in abdominal glands. Result: Death. Remarks: Tapped once; milky fluid, and 3 litres at necropsy; free fat; no leucocytes or other cells; thoracic duct involved in growth in origin.

Case 121 (Nathan Larrier, 1900). Age 65. Sex F. Disease: Carcinoma of ovary, metastases in abdominal glands, jaundice. Result: Death. Remarks: 2.5 litres; yellowish milky fluid found at necropsy; free fat; leucocytes, endothelial cells, cancer cells; bilateral hydrothorax; thoracic duct involved at origin.

Case 122 (Jousset, 1900). Age 38. Sex F. Disease: General lymphatic tuberculosis. Result: Death. Remarks: Chylous ascites found at necropsy; bilateral chylothorax; blood serum opalescent; thoracic duct normal.

Case 123 (Jousset, 1900). Age 65. Sex M. Disease: Atrophic cirrhosis of liver. Result: Death. Remarks: Tapped 18 times; last time only, milky fluid contained red cells and leucocytes.

Case 124 (Bernard, cited by Jousset, 1900). Age 42. Sex F. Disease: ? Atrophic cirrhosis of liver. Remarks: Tapped twice; 24 litres; opalescent fluid.

Case 125 (Witte, 1901). Age adult. Sex F. Disease: ? Thrombosis of thoracic duct. Result: Recovered. Remarks: Tapped 59 times from June 1896 to Oct. 1898, each time 6-12 litres; about 700 litres; milky fluid containing free fat; chylothorax.

Case 126 (Lea, 1901). Age 58. Sex F. Disease: Pelvic sarcoma, chronic peritonitis. Result: Recovered. Remarks: Laparotomy; 3.9 litres; milky fluid; drained for 6 days; no reaccumulation of fluid; well 4 years later; contains free fat and leucocytes.

Case 127 (Souques, 1902). Age 61. Sex M. Disease: Atrophic cirrhosis of liver. Result: Death. Remarks: Tapped twice; 28 litres; post mortem 10 litres; milky fluid; probably free fat; leucocytes.

Case 128 (Achard and Laubry, 1902). Age 44. Sex M. Disease: Atrophic cirrhosis of liver. Result: Death. Remarks: Tapped 4 times; 23 litres; clear yellow fluid; later tapped 3 times; 26.5 litres; milky fluid containing free fat, lymphocytes, and mononuclear cells, with fat globules; thoracic duct normal; mesentery shrunken; blood serum not opalescent; right chylothorax.

Case 129 (Achard and Laubry, 1902). Age 65. Sex M. Disease: Carcinoma of colon, metastases in liver, cirrhosis of liver (alcoholic). Result: Death. Remarks: Tapped once; 3 litres; latescent fluid; contains free fat, red cells, mononuclear leucocytes, and lymphocytes.

Case 130 (Menetier and Gauckler, 1902). Age 53. Sex F. Disease: Carcinoma of stomach, metastatic deposits in lung (thrombosis of vessels). Result: Death. Remarks: 4 litres; milky fluid obtained post mortem; contains free fat; cells containing fat; thoracic duct cancerous throughout whole length; bilateral chylothorax.

Case 131 (Pagenstecher, 1902). Age 47. Sex F. Disease: Chronic peritonitis. Result: Recovered. Remarks: Tapped twice and at laparotomy; 3.8 litres; milky fluid; free fat; a few leucocytes; lymph radicles of mesentery dilated and some cystic with milky fluid; thoracic duct not obstructed in abdomen.

Case 132 (Mosse, 1902). Age 68. Sex F. Disease: Chronic parenchymatous nephritis, pulmonary tuberculosis, amyloid disease, morbus cordis. Result: Death. Remarks: Tapped twice; 3.5 litres; milky fluid; contains leucocytes and granular material.

Case 133 (Hutchison, 1902). Age 32. Sex M. Disease: Ascites (milky). Result: Recovered. Remarks: Tapped once; fluid showed a creamy layer on standing; chylous; free fat.



Case 134 (Hutchison, 1902). Age 46. Sex M. Disease: Chronic nephritis. Result: Death. Remarks: First tapping clear fluid; later milky pseudo-chylous; no free fat.

Case 135 (Burgess, 1903). Age 59. Sex M. Disease: Carcinoma of pancreas. Result: Death. Remarks: Tapped 3 times; 15.6 litres; milky fluid; free fat, leucocytes, and granular cells; thoracic duct obstructed.

Case 136 (Combey and McKibbin, 1903). Age 61. Sex M. Disease: Cellulitis of right leg. Result: Death. Remarks: Tapped once; 3.97 litres; milky fluid; contains minute granules microscopically; lacteals in abdomen dilated and varicose; thoracic duct obstructed; left hydrothorax.

Case 137 (Joachim, 1903). Disease: Cirrhosis of liver. Remarks: Tapped; 0.6 litre; milky fluid; hydropericardium.

Case 138 (Clarkson, 1903). Age 25. Sex M. Disease: Carcinoma of liver. Result: Death. Remarks: Tapped once; 5.68 litres; 1.7 litres post mortem; yellowish milky fluid; contains free fat and cells containing fat; thoracic duct involved in growth at origin; left chylothorax and right hydrothorax.

Case 139 (Wolff, 1903). Disease: Malignant disease of abdomen. Result: Death. Remarks: Tapped 8 times; 3 litres; milky fluid.

Case 140 (Bernert, 1903). Age 51. Sex M. Disease: Lymphosarcoma of abdominal glands, generalized metastatic growths. Result: Death. Remarks: Tapped twice; 16.5 litres; milky fluid; no free fat; at autopsy peritoneal fluid, reddish yellow colour, containing free fat, granular debris, cells containing fat, and red cells; lymphatic vessels of mesentery distended; right chylothorax; left hydrothorax, which became later a chylothorax.

Case 141 (Bernert, 1903). Age 30. Sex F. Disease: Carcinoma of ovary, peritoneal metastases, fibro-purulent peritonitis. Result: Death. Remarks: Tapped 3 times; 28.2 litres; turbid milky fluid; no free fat, but finely granular debris; left hydrothorax.

Case 142 (Polyakoff, 1903). Age 24. Disease: Morbus cordis, syphilitic enlargement of liver. Result: Death. Remarks: Tapped 5 times in 6 months; milky fluid; no free fat, but finely granular debris, a few leucocytes, and endothelial cells; thoracic duct not obstructed; no nephritis.

Case 143 (Palmabo, 1904). Age 28. Sex M. Disease: Tuberculous peritonitis, chronic interstitial nephritis. Result: Death. Remarks: Tapped; milky fluid; chylous; right chylothorax; thoracic duct not obstructed; ? rupture or dilatation of chyle vessels.

Case 144 (Landolfi, 1904). Disease: Tuberculous peritonitis. Remarks: Tapped; milky fluid.

Case 145 (von Tabora, 1904). Disease: Carcinoma of stomach, secondary deposits in glands and peritoneum. Result: Death. Remarks: Tapped twice; 13.5 litres; yellowish milky fluid; microscopically free fat; chylous.

Case 146 (Nehr Korn and Kaposi, 1904). Age 6. Sex M. Disease: Tuberculous peritonitis. Remarks: Tapped once; clear fluid; second tapping milky; laparotomy; diagnosis confirmed; drainage; recovery; rheumatic fever and morbus cordis before onset of peritonitis; bilateral chylothorax.

Case 147 (Zorab and Daw, 1904). Age 35. Sex F. Disease: Sarcoma (? primary in ovary). Result: Death. Remarks: Tapped twice; ordinary ascitic fluid; tapped 4 times later; all milky; many litres; free fat; bilateral chylothorax; ascites and chylothorax disappeared before death.

Case 148 (Lambrior, 1905). Age 54. Sex M. Disease: Atrophic cirrhosis of liver (acute type). Result: Death. Remarks: Tapped once; 16 litres; 12 litres at necropsy; milky fluid; contains free fat; thoracic duct normal.

Case 149 (Lambrior, 1905). Age 51. Sex M. Disease: Atrophic cirrhosis of liver (acute type). Result: Death. Remarks: Tapped once; 14 litres; milky fluid; characters same as preceding; right chylothorax.

Case 150 (Taylor and Fawcett, 1905). Age 31. Sex M. Disease: Chronic nephritis, anasarca. Result: Death. Remarks: Tapped 6 times; milky fluid; no free fat, but finely granular material; legs tapped; clear fluid at first; later milky fluid; thoracic duct normal; bilateral chylothorax at autopsy.

Case 151 (J. G. Wilson, 1905). Age 35. Sex F. Disease: Sarcoma of retroperitoneal

glands, morbus cordis. Result: Death. Remarks: 1902: radical operation for femoral hernia, then found to have chyloform ascites, ? due to tuberculosis of peritoneum; 1905: milky fluid obtained postmortem, 1-2 litres, containing free fat and cellular elements of which 70 % were lymphocytes, 29 % large mononuclear, 1 % neutrophiles; chylothorax.

Case 152 (Boston, 1905). Age 11. Sex M. Disease: Tuberculous peritonitis. Result: Death. Remarks: 2 litres of milky fluid at autopsy; thoracic duct patulous throughout whole length; bilateral hydrothorax; hydropericardium.

Case 153 (McKelway, cited by Boston, 1905). Age 33. Sex F. Disease: Abortion (third month), sepsis. Result: Recovered. Remarks: Tapped; 0.5 litre; chylous fluid.

Case 154 (Sommer, 1906). Age 51. Sex F. Disease: Carcinoma of ovary, metastases in retroperitoneal glands and liver and other organs. Result: Death. Remarks: Tapped 5 times; 9.5 litres; yellowish milky fluid; free fat; right chylothorax; thrombosis of inferior vena cava; thoracic duct carcinomatous throughout and compressed above receptaculum chyli.

Case 155 (Zypkin, 1906). Age 22. Sex M. Disease: Chronic tuberculous peritonitis, nephritis, colitis ulcerosa, amyloid disease of liver, spleen, and kidneys. Result: Death. Remarks: Tapped twice; 8.05 litres; first tapping milky; no free fat; second, sero-haemorrhagic fluid.

Case 156 (Zypkin, 1906). Age 28. Sex F. Disease: Chronic tuberculosis, amyloid disease, atrophica universalis summa. Result: Death. Remarks: Tapped 4 times; 20.5 litres; milky; last tapping 7 litres of ordinary serous fluid; ascitic fluid at necropsy milky; right chylothorax.

Case 157 (Herczel, 1906). Age 26. Sex F. Disease: Pyonephrosis (left side), nephrectomy. Remarks: Swelling of abdomen after operation, ? injury to chyle vessels; tapped twice; 15.5 litres; first tapping milky; second a darker yellowish fluid with a thick cream; contains free fat and many lymphocytes; increase in fat content of second sample due to a milk diet.

Case 158 (Ghedini, 1906). Age 62. Sex M. Disease: Carcinoma of pancreas, metastases in peritoneum and liver. Result: Death. Remarks: Tapped 5 times in 3 months; last tapping only was milky, others clear; microscopically scanty cellular elements, some of which contain fat.

Case 159 (Stroh, 1907). Age 62. Sex F. Disease: Cirrhosis of liver, chronic interstitial nephritis, amyloid disease. Result: Death. Remarks: Tapped 3 times; 6.5 litres; milky fluid; no free fat; thoracic duct not obstructed.

Case 160 (G. Moorhead, 1907). Age 47. Sex F. Disease: Cirrhosis of liver, chronic peritonitis, nephritis. Remarks: Tapped 8 times; milky fluid; no free fat or granules.

Case 161 (Massing, 1907). Disease: Tuberculosis of ileum and colon, chronic parenchymatous nephritis, enlargement of liver, tuberculosis of lungs. Result: Death. Remarks: Tapped once; 2.2 litres, and a large quantity of milky fluid post mortem; no free fat; some cells with fatty degeneration; thoracic duct and chyle vessels normal; bilateral chylothorax and chylopericardium.

Case 162 (Massing, 1907). Age 39. Sex F. Disease: Lymphadenoma. Remarks: Tapped many times; a clear fluid; later 12 litres of turbid milky yellow fluid; no free fat, but epithelial cells and red cells; left hydrothorax.

Case 163 (Massing, 1907). Age 63. Sex M. Disease: Carcinoma of stomach, metastases in peritoneum and liver. Remarks: Tapped once; 4 litres; turbid milky fluid; no free fat; a few epithelial cells and red cells.

Case 164 (Leschtschinski, 1907). Age 57. Sex M. Disease: Carcinoma of pancreas, metastases in mesenteric glands. Result: Death. Remarks: Tapped 4 times; 35 litres; milky fluid; 7.5 litres post mortem; contains free fat, endothelial cells, leucocytes, and cells undergoing fatty degeneration; thoracic duct dilated at origin and obstructed by a thrombus at diaphragmatic opening, while the upper part of the duct is dilated and the walls thickened; left chylothorax and left hydrothorax post mortem.

Case 165 (Dock, 1907). Age 59. Sex M. Disease: Lymphosarcoma. Result: Death. Remarks: Tapped; 2.45 litres; a thin milky fluid containing lymphocytes; thoracic duct obstructed by growth throughout length; right chylothorax.

Case 166 (Fellner, 1907). Age 26. Sex M. Disease: ? Lymphadenoma. Result:

Death. Remarks: Milky fluid obtained at necropsy; thoracic duct not obstructed; normal.

Case 167 (Strzyzowski, 1908). Age 56. Sex F. Disease: Carcinoma of caecum, metastases in liver. Result: Death. Remarks: Tapped June 1906; 3.14 litres; milky fluid; free fat present; August 1901, had had an ileocolostomy for growth; May 1904, gastroenterostomy for growth in stomach; died July 1906.

Case 168 (Strzyzowski, 1903). Age 60. Sex F. Disease: Growth at the hilum of the liver. Result: Death. Remarks: Milky fluid removed from abdomen.

Case 169 (Moehle, 1896). Age 42. Sex M. Disease: Carcinoma of stomach, metastases in peritoneum and retroperitoneal glands. Result: Death. Remarks: Milky fluid; chylous.

Case 170 (Winkler, 1900). Age 43. Sex F. Disease: Carcinoma of ovary. Result: Death. Remarks: Tapped; 5 litres; also fluid obtained at necropsy; thoracic duct partly surrounded by growth.

Case 171 (Author's I, 1910). Age 43. Sex M. Disease: Chronic nephritis. Result: Recovered. Remarks: Tapped twice; 21.86 litres; milky fluid; no free fat; pseudo-chylous.

Case 172 (Author's II, Dr. T. J. Horder, 1910). Age 42. Sex F. Result: Recovered. Remarks: Tapped 4 times; milky fluid; many litres; free fat on one occasion; pseudo-chylous.

Case 173 (Author's III, Dr. J. M. Cowan, 1910). Age 61. Sex M. Disease: Chronic nephritis, ? cirrhosis of liver. Result: Recovered. Remarks: Tapped many times; milky fluid; no free fat; pseudo-chylous.

#### B. SYNOPSIS OF THE RECORDED CASES OF CHYLOUS AND PSEUDO-CHYLOUS HYDROTHORAX.

Case 1 (Rokitansky, 1865). Age 62. Sex M. Disease: Morbus cordis. Result: Death. Remarks: Autopsy; bilateral chylothorax; milky fluid; dilatation of pleural lymphatics; thoracic duct obstructed; walls dilated; chylous ascites.

Case 2 (Gueneau de Mussy, 1874). Age 50. Sex M. Disease: Left pleural effusion of 15 years' standing. Result: Recovered. Remarks: Tapped 3 times; about 5 litres; milky fluid; free fat but no cells.

Case 3 (Gueneau de Mussy, 1874). Age 23. Sex M. Disease: Haemoptysis (probably pulmonary tuberculosis), left pleural effusion. Result: Recovered. Remarks: Tapped many times; left pleura, greenish opaque fluid; contains free fat.

Case 4 (Quinke, 1875). Age 50. Sex M. Disease: Traumatic chylothorax, right side, fractured ribs 7-9, left side. Result: Death. Remarks: Tapped 3 times; 5.8 litres; right pleura, 7 litres post mortem; left hydrothorax; 100 c.c.; chylous ascites.

Case 5 (Pelletier, 1875). Age 24. Sex F. Disease: Gastro-intestinal disorder, milky vomit, and milky diarrhoea. Result: Recovered. Remarks: Tapped; milky fluid; bilateral chylothorax.

Case 6 (Boegehold, 1878). Age 43. Sex M. Disease: Carcinoma of stomach, metastases in lungs. Result: Death. Remarks: Tapped 3 times; autopsy, 5.4 litres; left pleura, milky fluid; contains free fat.

Case 7 (Debove, 1881). Age 63. Sex M. Disease: Left pleural effusion following exposure. Result: Sudden death. Remarks: Tapped once; 0.75 litre; autopsy; 2 litres; milky fluid; contains free fat, cholesterin, and leucocytes.

Case 8 (Krabbel, 1885). Age 16. Sex M. Disease: Fracture of ninth dorsal vertebra, rupture of thoracic duct. Result: Death. Remarks: Autopsy; right pleural cavity; 6 litres; milky fluid; chylous.

Case 9 (Hampell, 1890). Disease: Pleurisy; milky fluid; no details.

Case 10 (Neuenkirehen, 1890). Age 47. Sex F. Result: Recovered. Remarks: Left chylothorax for 5 years, then right chylothorax in 1884; tapped 9 times (1889-90); milky yellow fluid.

Case 11 (Chelchowski, 1890). Age 34. Sex M. Disease: Phthisis, fracture of fifth and sixth left ribs. Result: Recovered. Remarks: Right hydrothorax for 2 years previous to injury; right chylothorax; tapped many times; milky fluid.

Case 12 (Chelchowski, 1890). Age 53. Sex M. Disease: Carcinoma of stomach, metastases in thoracic glands. Result: Death. Remarks: Left chylothorax.

Case 13 (Reichenbach, 1891). Age 58. Sex M. Disease: Lymphosarcoma. Result: Death. Remarks: No autopsy; chyloform; chyloform ascites; tapped; 2.25 litres.

Case 14 (Reichenbach, 1891). Sex M. Disease: Lymphosarcoma. Result: Death. Remarks: Tapped many times; bilateral chylothorax; chylous ascites.

Case 15 (Zawadzki, 1891). Age 67. Sex F. Disease: Carcinoma of stomach, generalized carcinosis of peritoneum. Result: Death. Remarks: Milky fluid found at autopsy; chylothorax; thrombosis of innominate and left subclavian vein; chylous ascites.

Case 16 (Fraenkel, 1891). Age 40. Sex M. Disease: Carcinoma of pleura, meningitis. Result: Death. Remarks: Tapped; right pleura, milky fluid.

Case 17 (Martin, 1891). Age 31. Sex F. Disease: Miliary tubercle of lung. Result: Death. Remarks: Tapped 5 times; 7.9 litres; milky fluid; chylous.

Case 18 (Leydhecker, 1893). Age 39. Sex F. Disease: Carcinoma of the pylorus, metastases in liver and lungs. Result: Death. Remarks: Tapped once; left hydrothorax; 300 c.c.; autopsy; bilateral chylothorax; 1500 c.c.; chylous fluid; thoracic duct infiltrated with growth; pleural lymphatics dilated; chylous ascites.

Case 19 (Turney, 1893). Age 54. Sex M. Disease: Carcinoma of the pylorus. Result: Death. Remarks: Autopsy; right chylothorax; 2 pints; milky fluid; chylous; thrombosis of left subclavian vein; ascites.

Case 20 (Bargebuhr, 1894). Age 42. Sex M. Disease: Carcinoma of peritoneum, metastases in left lung and liver. Result: Death. Remarks: Autopsy; 0.75 litre; milky greyish fluid; somewhat viscid; thrombosis of left subclavian vein.

Case 21 (Port, 1894). Age 35. Sex M. Disease: Injury to spine, rupture of thoracic duct. Result: Recovery in 4 weeks. Remarks: Tapped once; right chylothorax; 3 litres; reddish milky fluid; microscopically free fat and blood cells.

Case 22 (Lockhart Gillespie, 1894). Disease: Lymphadenoma. Remarks: Chylothorax; thoracic duct obstructed.

Case 23 (Senator, 1895). Age 47. Sex F. Disease: Carcinoma of ovary, metastases in mesenteric glands. Result: Death. Remarks: Autopsy; bilateral chylothorax; same characters as ascitic fluid; thoracic duct obstructed.

Case 24 (Lenhartz, 1895). Disease: Peritoneal carcinoma. Result: Death. Remarks: Autopsy; left chylothorax.

Case 25 (Lenhartz, 1895). Disease: Carcinoma of bronchus. Result: Death. Remarks: Chylothorax.

Case 26 (Bargebuhr, 1895). Age 31. Sex F. Disease: Carcinoma of stomach, metastases in lungs. Result: Death. Remarks: Autopsy; 0.75 litre; milky greyish fluid; somewhat viscid.

Case 27 (Erb, 1896). Age 20. Sex M. Disease: Lymphangiectasis of left leg, and abdominal cavity and dilatation of thoracic duct. Result: Death. Remarks: Tapped 8 times; 30 litres from right pleural cavity; yellowish milky fluid; microscopically many fine granules in active molecular movement; chylous fluid.

Case 28 (Corselli and Frisco, 1896). Disease: Small-cell sarcoma, retroperitoneal growth. Result: Death. Remarks: Tapped; bilateral chylothorax; autopsy; right pleura, 1.4 litres; left pleura, 0.4 litre; milky fluid; same as ascitic fluid.

Case 29 (Corselli and Frisco, 1896). Age 24. Sex M. Disease: Malignant disease of abdomen, metastasis in liver. Result: Death. Remarks: Milky fluid obtained from both pleural cavities at post-mortem; ascites.

Case 30 (Merklen, 1897). Age 61. Sex F. Disease: Cirrhosis of liver (atrophic), (traumatic injury to lacteals). Remarks: Left chylothorax; like ascitic fluid.

Case 31 (Rotmann, 1897). Age 30. Sex M. Disease: Tuberculosis of lung, right pneumothorax. Remarks: Tapped twice; 1.3 litres; right pleural cavity; turbid milky fluid; chyloform; fat globules of varying size; cells containing fat.

Case 32 (Sarrazin, 1897). Sex F. Disease: Cystocarcinoma of ovary, metastases in abdominal glands. Result: Death. Remarks: Yellow turbid fluid obtained from pleural cavity at necropsy; thoracic duct permeable in thorax, not in abdomen; chylous ascites.

Case 33 (Mackie Whyte, 1897). Age 21. Sex F. Disease: Morbus cordis, ? tuberculosis. Result: Death. Remarks: Tapped 8 times; bilateral; microscopically no fat; a few leucocytes and finely granular debris; chylous ascites and chylopericardium.

Case 34 (Simon, 1899). Age 20. Sex M. Disease: Lymphangiectasis of leg and visceral lymphatics. Result: Death. Remarks: Tapped; first time clear fluid; later milky; right pleura; thoracic duct compressed by the convoluted lymph-vessels.

Case 35 (Hahn, 1899). Age 32. Sex M. Disease: Traumatic, rupture of thoracic duct. Result: Death. Remarks: Tapped 10 times; 30.3 litres; milky fluid; right pleural cavity; autopsy, 7 litres; free fat.

Case 36 (Michelli and Mattiolo, 1899, 1900). Age 60. Sex M. Disease: Cirrhosis of liver, chronic peritonitis. Result: Death. Remarks: Yellowish milky fluid; free fat; chylous ascites.

Case 37 (Michelli and Mattiolo, 1899, 1900). Remarks: Bilateral milky effusions; no free fat; endothelial cells containing fat; chylous ascites.

Case 38 (Jousset, 1900). Age 38. Sex F. Disease: General lymphatic tuberculosis. Result: Death. Remarks: Left pleura tapped 3 times; 3.4 litres; right pleura tapped once; 1 litre; thoracic duct normal; chylous ascites.

Case 39 (Jousset, 1900). Age 21. Sex F. Disease: ? New growth of pleura. Remarks: Left pleura tapped 4 times; 4 litres; milky fluid; contained refractile granules; no cells.

Case 40 (Witte, 1901). Age adult. Sex F. Disease: ? Thrombosis of thoracic duct. Result: Recovered. Remarks: Tapped 16 times over a period of six months; contains free fat, many red cells and a few leucocytes; chylous ascites.

Case 41 (S. Mutermileh, 1902). Age  $\frac{1}{2}$ . Sex F. Disease: Injury to right side of chest. Remarks: Tapped once; 115 c.c.; right pleural cavity; milky fluid; microscopically finely granular material soluble in ether, forming large drops of fat; cells containing fat; chylous.

Case 42 (Menetier and Gauekler, 1902). Age 53. Sex F. Disease: Carcinoma of stomach, metastases in lungs, venous thrombosis of vessels at root of neck. Result: Death. Remarks: Bilateral chylothorax found post mortem; organized thrombus in left subclavian and jugular veins; recent thrombus in right subclavian and jugular veins; distension of visceral lymphatics of lungs; thoracic duct cancerous throughout; chylous ascites.

Case 43 (Strauss, 1902). Age 44. Sex M. Disease: Tuberculosis of lungs. Result: Death. Remarks: Tapped once; 1.6 litres; left pleural cavity; milky fluid; (ascites); right pleural cavity; hydrothorax.

Case 44 (Aehard and Laubry, 1902). Age 44. Sex M. Disease: Atrophic cirrhosis of liver. Result: Death. Remarks: Right pleural cavity; milky fluid; chylous ascites.

Case 45 (Bayer, quoted by Pagenstecher, 1902). Disease: Tuberculous glands in neck, ? tuberculosis of thoracic duct. Remarks: Right chylothorax; chylous ascites.

Case 46 (Clarkson, 1903). Age 25. Sex M. Disease: Carcinoma of liver. Result: Death. Remarks: At autopsy, left pleural cavity full of milky fluid; microscopically large droplets of free fat, and cells containing fat; thoracic duct involved in growth in abdomen; right hydrothorax; chylous ascites.

Case 47 (Bernert, 1903). Age 51. Sex M. Disease: Lymphosarcoma, abdominal glands involved, generalized metastases. Result: Death. Remarks: Right pleural cavity tapped; milky fluid; 1 litre at post-mortem; left pleural cavity tapped, clear fluid; second tapping, milky fluid; at autopsy, 0.5 litre; brownish fluid; ascites.

Case 48 (Zorab and Daw, 1904). Age 35. Sex F. Disease: Sarcoma, ? primary in ovary. Result: Death. Remarks: Tapped once; milky fluid; left pleural cavity; exploratory puncture, milky fluid; right pleural cavity; bilateral chylothorax disappeared before death; chylous ascites.

Case 49 (Wilson, 1905). Age 35. Sex F. Disease: Lymphosarcoma, abdominal glands involved; morbus cordis. Result: Death. Remarks: Tapped several times over a period of 17 months; microscopically finely granular emulsion of fat; cellular content; 76 % lymphocytes; 22 % mononuclear; 2 % polynuclear neutrophiles; chylous ascites.

Case 50 (Zypkin, 1906). Age 28. Sex F. Disease: Chronic tuberculosis, amyloid disease. Result: Death. Remarks: Tapped; 0.4 litre; milky greenish fluid from right side; same type of fluid at necropsy; chylous ascites.

Case 51 (Ghedini, 1906). Age 47. Sex M. Disease: Chronic tuberculosis of lungs and peritoneum. Remarks: Tapped; 500 c.c.; right pleural cavity; milky fluid; contains free fat, a few leucocytes, and endothelial cells containing fat; cholesterol crystals and fatty acid crystals; sero-fibrinous effusion in peritoneum.

Case 52 (Ghedini, 1906). Age 50. Sex M. Disease: Tuberculous broncho-pneumonia. Remarks: Milky fluid from pleural cavity; contains free fat, leucocytes, and endothelial cells.

Case 53 (Leschtschinski, 1907). Age 57. Sex M. Disease: Carcinoma of pancreas, metastases in abdominal glands. Result: Death. Remarks: Tapped; left pleural cavity; 1.5 litres; milky fluid; 1.5 litres obtained post mortem; not milky, but sero-haemorrhagic; thoracic duct dilated at upper part; chylous ascites.

Case 54 (Dock, 1907). Age 59. Sex M. Disease: Lymphosarcoma. Result: Death. Remarks: Tapped once; right side; milky fluid; microscopically lymphocytes; no record of free fat; at autopsy, right side contained a turbid greyish fluid.

Case 55 (L. von Ketley, 1907). Age 26. Sex M. Disease: No diagnosis, not malignant or tuberculous. Result: Recovered. Remarks: Right pleural cavity tapped several times; first milky, then serous, and finally opalescent; all fluids except first contained free fat; under observation for 2½ years.

Case 56 (L. von Ketley, 1907). Age 36. Sex F. Disease: Lymphosarcoma of mediastinum, thymic in origin, metastases in lungs, liver, and cervical glands. Result: Death. Remarks: Right pleural cavity contained milky fluid ante mortem, but serous fluid post mortem; left pleural cavity contained, post mortem, 40 c.c. of opalescent fluid; left innominate vein obliterated by growth; thoracic duct normal.

Case 57 (Fellner, 1907). Age 26. Sex M. Disease: ? Lymphadenoma, enlarged lymph glands, liver, and spleen. Remarks: Milky fluid found at necropsy; right chylothorax; thoracic duct normal, not compressed; chylous ascites.

Case 58 (Ormerod, J. A., 1907). Age 13. Sex M. Disease: Lymphadenoma. Result: Recovered. Remarks: Tapped 3 times; 6.75 pints; right pleural cavity; microscopically fat globules in fine suspension; a few mononuclear and endothelial cells.

Case 59 (Massing, 1907). Disease: Tuberculosis of lungs and intestines, chronic nephritis, enlargement of liver. Result: Death. Remarks: Bilateral chylothorax; turbid milky fluid obtained post mortem; same characters as peritoneal fluid; chylopericardium; thoracic duct normal.

Case 60 (Buchtala, 1910). Sex M. Disease: Fracture of left clavicle, probable injury to thoracic duct. Result: Not stated. Remarks: Tapped once; 0.5 litre; left pleura; yellow milky fluid; contains finely emulsified fat.

#### C. SYNOPSIS OF THE RECORDED CASES OF MILKY PERICARDIAL EFFUSIONS.

Case 1 (G.-Besanez). Disease: No information, chemical analyses alone given.

Case 2 (Wachsmuth). Disease: No information, chemical analyses alone given.

Case 3 (Hoppe-Seyler). Disease: No information, chemical analyses alone given.

Case 4 (Hasebroek, 1888). Sex M. Disease: ? Rupture of chyle vessel. Remarks: Autopsy; 22.6 c.c.; milky turbid fluid; microscopically fine chyle-like granules.

Case 5 (Fraenkel, 1892). Age 44. Sex M. Disease: Primary carcinoma of pleura. Remarks: Autopsy; 0.5 litre; blood-stained milky fluid.

Case 6 (Mackie Whyte, 1897). Age 21. Sex F. Disease: Morbus cordis (? tuberculosis). Result: Death. Remarks: No autopsy; milky fluid aspirated post mortem.

Case 7 (Calabrese, 1899). Disease: Morbus cordis (mitral stenosis).

Case 8 (Massing, 1907). Disease: Tuberculosis of lungs and intestines, chronic nephritis, enlargement of liver. Result: Death. Remarks: Chylopericardium found at necropsy; fluid having the same characters as the peritoneal effusion; bilateral chylothorax.

## REFERENCES

## HISTORICAL.

1. Bossu, *Journ. de Méd., Chir., Pharm.*, 1770, xxxiv. 283.
2. Broussais, *Hist. des phlegmasis ou inflamm. chron.*, 1831, vii, chap. iv.
3. Chomel, *Mém. de l'Acad. des Sciences*, 1710.
4. Cossium, cited by Lieutard.
5. Diemerbroeck, *Op. Omnia Anat. et Med.*, Utrecht, 1685.
6. Hughes, *Guy's Hosp. Reports*, Lond., 1841, vi. 297.
7. Lieutard, *Historia Anatomica Medica*, 1779, i. 257.
8. Littré, *Mém. de l'Acad. des Sciences*, 1710.
9. Lorain, *Compt. rend. Soc. de Biol.*, Ser. 2, 1858, 162.
10. Martin, *Journ. de Méd., Chir., Pharm.*, 1770, xxxiv. 555.
11. Milleret, *ibid.*, 1774, xlii. 237.
12. Monro, *Essay on Dropsy and its species*, 3rd Edit., 1765, 22.
13. Morton, *Phthisiologie*, 1705, 21.
14. Percival, *Essays Med., Philosoph. and Exp.*, 1788, ii. 177.
15. Poncy, *Observations in Surgery by Saviard*, Lond., 1669, 247.
16. Popham, *Dublin Quart. Journ. Med. Sci.*, 1854, xvii. 467.
17. Sandifort, *Observat. Anat. Pathol.*, Ludg. Batav., 1781, iv. 1-21.
18. Saviard, *Observations in Surgery*, Lond., 1701.
19. Scherb, *Haller. Diss. Abmorborum*, 1729, iii. 237.
20. Targioni, 1771, quoted by Bianchi, *Lo Sperimentale*, lvii. 71.
21. Truman-Abell, *Boston Med. and Surg. Journ.*, 1833, vii. 13.
22. Van Camp, *Ann. Soc. de Méd. d'Anvers*, 1843, 86.
23. Weaver, *Med., Surg. and Pharm. Repos.*, 1814, 377.

## 1860—PRESENT DAY.

24. Achard, *Bull. et Mém. de la Soc. de Méd. des hôp. de Paris*, 1896, xiii. 773-775.
25. Achard and Laubry, *ibid.*, 1902, 295 and 385.
26. Apert, *Bull. de la Soc. Anat. de Paris*, 1897, 5th Ser., xi. 187.
27. Ascoli, *Riv. critica clin. med.*, 1900, xxii.
28. Ballmann, *Centralb. f. Med. Wissensch.*, Berlin, 1876, xiv. 275-277.
29. Bargebuhr, *Deutsch. Archiv f. klin. Med.*, 1893, li. 161.
30. Bayer, *Mitt. aus den Grenzgebiet. der Med. und Chir.*, 1897, ii. 67.
31. Bergeret, *Journ. de l'Anat. et Physiol. norm. et path.*, Paris, 1873, ix. 586.
32. Bernard, cited by Jousset, *loc. cit.*
33. Bernert, *Arch. f. exp. Path. u. Pharm.*, 1903, xlix. 32-84.
34. Boston, *Journ. Amer. Med. Assoc.*, 1905, xlv. 513-518.
35. Bradshaw, *Liverp. Med. Chir. Journ.*, 1894, 252.
36. Brieger, *Charité-Annalen*, Berlin, 1883, viii. 109-123. (Paper written in 1881.)
37. Burgess, *Lancet*, Lond., 1903, i. 1740.
38. Cayley, *Trans. Path. Soc. Lond.*, 1866, xvii. 163.
39. Ceconi, *Il Morgagni*, 1897, xxxix. 69-105.
40. Ceconi, *Munch. med. Woch.*, 1899, 477-480; also *Clin. med. ital.*, 1898.
41. Clarkson, *Lancet*, Lond., 1903, i. 961.
42. Combey and McKibbin, *Boston Med. and Surg. Journ.*, 1903, exlviii. 109.
43. Corselli and Frisco, *La rif. medica*, 1896, 630.
44. Croom, H., *Lancet*, Lond., 1900, i. 938 and 1791.
45. Czerny, *Munch. med. Woch.*, 1898, xlv. 31.
46. Day, *N. Y. Med. News*, 1897, lxxxi. 469.
47. Dock, *Amer. Journ. Med. Sci.*, 1907, N. S. cxxxiv. 634-643.
48. Duffey, *Trans. Acad. Med. Ireland*, 1886, iv. 297.

49. Eisenschütz, *Wiener klin. Rundschau*, 1895, 785 and 805.
50. Enzmann, cited by Leydhecker, 1883.
51. Eshner, *Proc. Path. Soc. Philad.*, 1899.
52. Fellner, *Wiener klin. Woch.*, 1907, xx, 1522.
53. Friedrich, quoted by Quincke, 1875.
54. Gaucher, cited by Veil, 1882.
55. Ghedini, *Gazz. d. osp. Milano*, 1906, xxxvii, 875.
56. Gross, *Arch. f. exp. Path. u. Pharm.*, Leipzig, 1900, xliv, 179-185.
57. Haasz, *Časopis čes lékařů*, 1896, Nos. 47 and 48 (ref. in *Centralblatt f. Allg. Path.—Anat. Path.* V. ix, 1897).
58. Haswell, *Liverpool Med. Chir. Journ.*, 1889, ix, 65-69.
59. Hektoen, *Virchow's Arch. f. Path. Anat. u. Physiol.*, 1894, cxxxv, 357.
60. Herczel, *Ungarische medicin. Revue*, 1906, i, 337, &c.
61. Hirschler and Buday, *Orvosi hetilap*, Budapest, 1889, 424.
62. Hirtz and Luys, *Bull. et Mém. de la Soc. de Méd. des hôp. de Paris*, 1897, 1148-1158.
63. Hödlmoser, *Wiener klin. Woch.*, 1898, 1149-1152.
64. Hutchison, *Trans. Path. Soc. Lond.*, 1902, liii, 274.
65. Joachim, *Münch. med. Woch.*, 1903, ii, 1915-1916.
66. Jones, *Trans. Path. Soc. Lond.*, 1875, xxvi, 227.
67. Jousset, *Thèse de Paris*, 1901.
68. Kahn, *Bull. méd.*, 1900, No. 28.
69. Kamienski, *Jahrb. f. Kinderheilk.*, 1896, xli, 404-441.
70. Klebs, *Handb. der Path. Anat.*, 1869, i, 322.
71. Lambrior, *Rev. de Méd.*, Paris, 1905, xxv, 607-619.
72. Landolfi, *Gaz. d. osped.*, 1904, No. 103.
73. Lea, *Lancet*, Lond., 1901, i, 398.
74. Lenhartz, *Text Book*, 1895, 320.
75. Leschtschinski, *Deutsch. med. Woch.*, 1907, xxxiii, 101-103.
76. Letulle, *Rev. de Méd.*, Paris, 1884, iv, 722.
77. Letulle, *ibid.*, 1885, v, 960-973.
78. Leydhecker, *Virchow's Arch. f. Path. Anat. u. Physiol.*, 1893, cxxxiv, 118-144.
79. Lion, *Arch. de Méd. exp. et d'Anat. path.*, 1893, v, 826-836.
80. Lücke-Klebs, *Virchow's Arch. f. Path. Anat. u. Physiol.*, 1867, xli, 1.
81. McKelway, cited by Boston, *loc. cit.*
82. Martin, *Trans. Path. Soc. Lond.*, 1891, xlii, 93.
83. Massing, *St. Petersb. Med. Woch.*, 1907, xxxii, 231-234.
84. Mehu, *Arch. gén. d. Méd.*, 1877, Ser. vi, xxx, 513.
85. Menetier and Gauckler, *Bull. et Mém. de la Soc. de Méd. des hôp. de Paris*, 1902, 897.
86. Merklen, *Semaine méd.*, Paris, 1897, xvii, 181.
87. Michelli and Mattiolo, *Wiener klin. Woch.*, 1900, 56-59; *Rivista Acad. d. Med.*, Torino, 1901.
88. Moehle, *Greifswald Diss.*, 1896.
89. Moorhead, *Dublin Journ. Med. Sci.*, 1907, cxxiii, 81-84.
90. Mosse, *Internat. Beitrag zur inn. Med.*, E. von Leyden, 1902, 70<sup>ter</sup> Geburtstag, ii.
91. Minkowski, *Arch. f. exp. Path. u. Pharm.*, 1886, xxi, 373-386.
92. Munson, *N. Y. Med. Record*, 1873.
93. Murphy, *Chylous Ascites* (Pamphlet), Washington, 1886.
94. Nathan Larrier, *Bull. méd.*, 1900.
95. Nehr Korn and Kaposi, *Beitrag z. klin. Chir.*, Tübingen, 1904, xliii, Suppl., 123.
96. Newcomb, *N. Y. Med. Record*, 1890, xxxvii, 183.
97. Nieuwondt and Rozenzweig, *Brit. Med. Journ.*, 1892, ii, 123.
98. Oppolzer, *Allg. Wiener Med. Zeit.*, 1861, vi, 142.
99. Pagenstecher, *Deutsch. Arch. f. klin. Med.*, 1901-2, lxxii, 105-160.
100. Palmabo, *Il Policlínico*, 1904.
101. Pelletier, *Journ. de Méd., Chir., Pharm.*, 1875, lxiii, 496.
102. Pirkner, *Inaug. Diss.*, Greifswald, 1895.



103. Poljakoff, *Berl. klin. Woch.*, 1900, xxxvii. 9.
104. Poljakoff, *Fortschr. der Med.*, 1903, xxi. 1081-1085.
105. Pounds, *Brit. Med. Journ.*, 1892, ii. 629.
106. Quincke, *Deutsch. Archiv f. klin. Med.*, 1875, xvi. 121-139.
107. Rabinowitz, *Inaug. Diss.*, Freiburg, 1887.
108. Recklinghausen, *Handb. d. Allg. Path. des Kreisl. u. der Ernährung*, in *Deutsch. Chirurg.*, 1883, ii. 98.
109. Reichenbach, *Virehow's Arch. f. Path. Anat. u. Physiol.*, 1891, cxxiii. 183-186.
110. Rendu, *Bull. et Mém. de la Soc. de Méd. des hôp. de Paris*, 1897, 1158 (discussion on No. 62).
111. Renvers, *Berl. klin. Woch.*, 1890, xxvii. 320-322.
112. Ringer, cited by Batty Shaw, *Journ. Path. Bact.*, Edinb. and Lond., 1900, vi. 339.
113. Rokitansky, *Pathol. Anatomy*, 1865, 3rd Edit., ii. 388.
114. Rotmann, *Zeit. f. klin. Med.*, Berlin, 1897, xxxi. 416-441.
115. Sainton, *Gaz. hebdom. de Méd. et de Chir.*, 1896, xlv. 61.
116. Sarrazin, *Diss. Göttingen*, 1897.
117. Schaller, cited by Rabinowitz, *Inaug. Diss.*, Freiburg, 1887.
118. Schramm, *Berl. klin. Woch.*, 1896, xxxiii. 955.
119. Schterbatscheff, *Russ. Arch. f. Path., klin. Med. u. Bact.*, 1900, x.
120. Secretan, *Rev. méd. de la Suisse*, Geneva, 1887, vii. 633.
121. Senator, *Charité-Annalen*, Berlin, 1885, x. 314.
122. Senator, *ibid.*, 1895, xx. 263.
123. Siredey (in discussion of No. 141).
124. Smidt, *Zeit. f. klin. Med.*, 1881, ii. 199-204; also Gutmann, *Berl. klin. Woch.*, 1880, 421.
125. Smith, quoted by Busey, *Amer. Journ. Med. Sci.*, 1889, xcvi. 563.
126. Smith, *Trans. Path. Soc. Lond.*, 1891, xlii. 100; also Curwen (Fenwick's case), *Brit. Med. Journ.*, 1891, ii. 598.
127. Sommer, *Deutsch. Arch. f. klin. Med.*, 1906, lxxxvii. 87-97.
128. Soupault, *Revue de Gynécol. et de Chir. abd.*, 1897, 10-29.
129. Souques, *Bull. et Mém. de la Soc. de Méd. des hôp. de Paris*, 1902, xix. 290.
130. Stern, *Virchow's Arch. f. Path. Anat. u. Physiol.*, 1880, lxxxi. 384.
131. Stevenson, *Guy's Hospital Rep.*, Lond., 1872, 3rd Ser., xvii. 231.
132. Straus, *Arch. de Physiol. norm. et path.*, Paris, 1886, 3rd Ser., vii. 367-392.
133. Stroh, *Charité-Annalen*, 1907, xxxi. 16-20.
134. Strzyzowski, *Zeit. f. Physiol. Chem.*, Strassburg, 1908-9, lviii. 92; also *Korresp.-Blätter schweiz. Ärzte*, 1903, xxxiii. 618-620.
135. v. Tabora, *Deutsch. med. Woch.*, 1904, xxx. 1595-1596.
136. Talma, *Berl. klin. Woch.*, 1900, xxxvii. 677.
137. Taylor and Fawcett, *Trans. Clin. Soc. Lond.*, 1905, xxxviii. 169.
138. Terrillon, *Bull. et Mém. de la Soc. de Chirurgie de Paris*, 1888, xiv. 626-632.
139. Turney, *Trans. Path. Soc. Lond.*, 1893, xlv. 1.
140. Vali, *Allgem. Wiener med. Zeit.*, 1892, xxxvii. 13.
141. Vaquez and Esmonet, *Bull. et Mém. de la Soc. de Méd. des hôp. de Paris*, 1900, xvii. 207.
142. Variot (in discussion of No. 141), 226-229.
143. Veil, *Thèse de Paris*, 1882.
144. Verdelli, *Il Morgagni*, 1894, xxxvi. 57, and 1897, xxxix. 800.
145. Weiss, *Centralbl. f. innere Med.*, 1894, xv. 665-669.
146. Whitla, *Brit. Med. Journ.*, 1885, i. 1089.
147. Whyte, *Edinb. Med. Journ.*, 1897, N. S. ii. 551-588.
148. Widai and Merklen, *Bull. et Mém. de la Soc. de Méd. des hôp. de Paris*, 1900, xvii. 200.
149. Wilhelms, *Corresp.-Blätt. d. ärztl. Vereins der Rheinlande*, 1875, No. 14. 13; also *Gazette hebdom.*, 1875.
150. Willis and Ormerod, *Trans. Path. Soc. Lond.*, 1868, xix. 199.
151. Wilson, J. G., *Amer. Journ. Med. Sci.*, 1905, N. S. cxxx. 629.
152. Witte, *Halle Diss.*, 1901.

153. Wolff, *Beitr. zur Chem., Physiol. u. Path.*, 1904, v. 208-210.
154. Zawadzki, *Gazeta lekarska*, 1891.
155. Zorab and Daw, *Guy's Hosp. Gaz.*, Lond., 1904, N.S. xviii. 464-465.
156. Zypkin, *Wiener klin. Woch.*, 1906.

## Pleural Effusions.

## HISTORICAL.

157. Bartolet, *Fabr. Bartoletti Methodus in Dyspnoeam seu de Respirationibus*, 1633, Bk. 4, iv, Part iii, chap. iii, 291.
158. Bass, *Observationes*, 1723.
159. Guiffart, cited by Bartholin, 1670, *Opusc. nova Anat.*, Frankfurt, 1670, 490.
160. Hoffmann, *Op. omnia phys. med.*, 1700, Suppl. II, Part II, 461.
161. Langlot, *Epist. Med. Centur. III*, 134, Epist. 37.
162. Rust, *Arch. f. Med.*, 1815.
163. Willis, cited by Monro, loc. cit., 1765.

## 1860—PRESENT DAY.

164. Bargebuhr, *Deutsch. Arch. f. klin. Med.*, Leipz., 1895, liv. 410-441.
165. Bayer, *Mittl. aus dem Grenzgeb. d. Med. u. Chir.*, 1897, ii. Parts I and II (cited by Pagenstecher, 1902).
166. Boegehold, *Berl. klin. Woch.*, 1878, 347.
167. Buchtala, *Zeit. f. physiol. Chem.*, Strassb., 1910, lxvii. 42.
168. Chelchowski, *Gazeta lekarska*, 1890.
169. Debove, *Bull. et Mém. de la Soc. des hôp. de Paris*, 1881, xviii. 49-62.
170. Erb, *Münch. med. Woch.*, 1896, 109-110.
171. Fraenkel, *Berl. klin. Woch.*, 1891, xxviii. 666; also *Deutsch. med. Woch.*, 1891, xvii. 786.
172. Gillespie, A. L., *Rep. Lab. Roy. Coll. Phys. Edin.*, 1897, v. 51.
173. Gueneau de Mussy, *Clinique médicale*, Paris, 1874, i. 58.
174. Hahn, *Deutsch. med. Woch.*, Leipz., 1899, xxv. 401-403.
175. Hampell, *St. Petersburger med. Woch.*, 1890, xv.
176. v. Ketley, *Wiener klin. Woch.*, 1907, 69-73.
177. Krabbel, *Centralbl. f. Chirurg.*, 1885, xii. 338.
178. Mutermilch, *Zeit. klin. Med.*, Berlin, 1902, xli. 123-134.
179. Neuenkirchen, *St. Petersburger Med. Woch.*, 1890, xv.
180. Ormerod, *St. Bart.'s Hosp. Journ.*, Lond., 1907, xiv. 98-100.
181. Port, *Deutsch. Zeit. f. Chirurg.*, Leipz., 1894, xxxix. 572.
182. Simon, *Grenzgebiete*, 1899.
183. Strauss, *Charité-Annalen*, Berlin, 1902, xxvi. ii. 89-105.

## Pericardial Effusions.

184. Calabrese, *Atti del X° Congresso della soc. di med.*
185. Fraenkel, *Verhandl. des XI. Congresses f. klin. Med. zu Leipzig*.
186. Gorup-Besanez, *Lehrbuch der Chemie*.
187. Hasebroek, *Zeit. f. physiol. Chem.*, Strassb., 1888, xii. 289.
188. Hoppe-Seyler, *Handbuch der physiologischen und pathologischen chemischen Analyse*.
189. Wachsmuth, *Virchow's Arch. f. Path. Anat. u. Physiol.*, 1854, vii. 334.

## Chemical.

190. Castaigne, *Arch. gén. de Méd.*, Paris, 1897, Ser. 8, vii. 666.
191. Christen, *Centralbl. f. innere Med.*, 1903, xxiv. 181.
192. Fawcett and Boycott, *Trans. Path. Soc. Lond.*, 1904, lv. 332-336.
193. Fichtner, *Deutsch. Arch. f. klin. Med.*, Leipz., 1889, xlv. 323, 334.

194. Joachim and Freund, *Zeit. f. physiol. Chem.*, Strassb., 1902, xxxvi. 407.
195. Jolles, *Wiener med. Woch.*, 1894, 2042-2043.
196. Mellanby, *Journ. of Physiol.*, Camb., 1907-8, xxxvi. 332.
197. Morawitz, *Beitr. zur chem. Physiol. u. Path.*, 1906, vii. 153.
198. Naunyn, *Arch. f. Anat. u. Phys.*, Leipz., 1865, 166.
199. Pascheles and Reichel, *Wiener klin. Woch.*, 1896, 311-314.
200. Rywosch, *Wiener med. Woch.*, 1901.
201. Vidal and Siccard, *Bull. et Mém. de la Soc. des hôp. de Paris*, 1896, xiii. 766.
202. Wilson and Williams, *Biochem. Journ.*, Liverpool, 1907, ii. 20.

#### Chyle.

203. Hamill, *Journ. Physiol.*, Camb., 1906-7, xxxv. 151-162.
204. Hoppe-Seyler, *Archiv f. d. ges. Physiol.*, Bonn, 1873, vii. 407.
205. Landois, *Lehrbuch d. Physiol.*
206. Owen Rees, *Phil. Trans. Roy. Soc. Lond.*, 1842, cxxxii. 81.
207. Panzer, *Zeit. f. physiol. Chem.*, 1900, xxx. 113.
208. Paton, *Journ. Physiol.*, Camb., 1890, xi. 109.

## ON PNEUMOCOCCAL PERITONITIS

### A PAPER BASED UPON A SERIES OF FIFTY-SEVEN CASES IN CHILDREN AND ONE IN AN ADULT<sup>1</sup>

BY HAROLD RISCHBIETH

#### *Introductory.*

PNEUMOCOCCAL peritonitis is a disease which appears to give rise to considerable differences of opinion as regards its clinical picture, its morbid anatomy, the path by which infection occurs, and the best method of treatment to be adopted. The condition seems to be considerably more common, at least in young children, than is often supposed, and it thus assumes some practical importance from the point of view of treatment, in addition to the scientific interest. On many points a good deal of obscurity exists, and it was felt that by the consideration of a series of cases, such as the fifty-seven<sup>2</sup> upon which this paper is based, some of this might perhaps be cleared up.

In only about half of these cases is the diagnosis by bacteriological examination certain, but of the others, though no bacteriological examination was made, it can be said that they were pneumococcal, owing to their clinical and morbid anatomical resemblance to the other cases, which was exact in all respects. The following general statements may be made:—(1) A considerable group of cases, showing, for the most part, multiple lesions, and comprising nearly one-third of cases in young children, seems to have escaped description and to have been omitted from statistics. It may be objected that these are as much cases of pneumonia, meningitis, arthritis, pericarditis, &c., as of peritonitis; but this is true of all other cases, though not to the same extent. The term pneumococcal 'peritonitis' may be applied to this group with as much approximation to accuracy as to the others. (2) The term 'primary', in whatever of several senses it may conceivably be employed, is inaccurate when applied to pneumococcal peritonitis. Thus, whether the term is used because no original diseased focus (appendix, Fallopian tube, &c.) is ever found on operation,<sup>3</sup> or is

<sup>1</sup> A thesis submitted for the degree of M.D., University of Cambridge.

<sup>2</sup> The complete accounts of these cases are recorded in a pamphlet in the Library of the Royal College of Surgeons. They are those of the London Hospital and of the Hospital for Sick Children, Great Ormond Street. For the courtesy of permission to refer to the cases I am indebted to Dr. Francis Warner, Dr. Percy Kidd, Dr. Bertrand Dawson, Dr. A. E. Garrod, Dr. A. F. Voelcker, Dr. D. B. Lees, Dr. F. E. Batten, Dr. F. Penrose, Mr. F. S. Eve, Mr. Arbuthnot Lane, Mr. F. J. Steward, Mr. Jonathan Hutchinson, Mr. Stansfield Collier, Mr. T. H. Kellock, Mr. E. M. Corner, Mr. T. H. Openshaw, Mr. H. M. Rigby, Mr. James Sherren, and Mr. G. E. Waugh.

<sup>3</sup> Cases of perforation of a viscus by ulceration, malignant or other, e. g. perforation of stomach, are not considered here. In the peritonitis resulting from such conditions the variety of organisms is great; the pneumococcus may, of course, be one. But the clinical and morbid

applied to cases in which there is no present evidence of pneumonia, or to imply that pneumococcal peritonitis occurs without other lesions, it is equally inaccurate. Pneumococcal peritonitis, like other varieties of general peritonitis, is always secondary, but not to a single focus of disease as in that following appendicitis, perforation of viscus, volvulus, &c., but to septicaemia, resembling one variety of tuberculous peritonitis in this respect. (3) The view that the condition is secondary to pneumococcal septicaemia is the only one that is capable of explaining all cases. It is unnecessary to regard any case (of the two more usual types for example) as 'peritonitis secondary to pneumonia' or as 'pneumonia secondary to peritonitis', for the two conditions are independent of one another but dependent upon the same cause, namely, pneumococcaemia.

Experimental medicine (7, 14, 15, 16, 18, 20, 22) teaches that cases of pneumonia are instances of pneumococcal septicaemia in which a secondary local lesion has arisen at the site of lowered resistance, the lung lesion being, in this view, analogous to such conditions as pneumococcal arthritis, epiphysitis periostitis, or to the subcutaneous pneumococcal abscesses which sometimes arise without evidence of lung lesion on the sites of bruises in children. The clinical and anatomical facts of the condition under consideration entirely support this view if all cases are considered and the whole history of the infection is regarded in each. The view, at first sight more probable, that the lung lesion is primary, corresponding to the site of inoculation in experiments on animals, is incompatible with cases in which pneumonia develops days after peritonitis and the analogous facts of conditions such as arthritis, periostitis, meningitis, and pneumococcal pyaemic abscesses. (4) Two forms are commonly described, the local and the general. These are not different varieties; the local cases represent the later stages of a general peritonitis in which the resistance has triumphed, and, either because this was great or because the dose or virulence was small, absorption and localization have occurred. There is no proof that these are produced by two different types of organism. (5) Pneumococcal peritonitis in adults, to judge from published cases and from three known to me, presents the same clinical and morbid anatomical features and types of case as in children; but there are the following differences:—It is rarer in adults than in children; the proportion of females to males affected is greater; adults represent on the whole more severe infections and their mortality is higher; association with other conditions is rarer in adults than in children, but when these occur they follow the frequency lines usual in pneumococcal infections—thus, e. g., arthritis is relatively more common and meningitis more rare in

anatomical conditions they show are quite different from 'pneumococcal peritonitis' of the ordinary type, and differ in no way clinically from cases of perforation of viscus due to other organisms. The same is true of pyosalpinx or perimetritis. In the case of malignant growths, e. g. of stomach (and perhaps, also, of some of the other conditions), the association is sometimes, as it were, accidental; for any case of cancer is predisposed to pneumonia or other pneumococcal infection, and, to judge from accounts, it appears that, at least in some cases, the peritonium becomes infected in the usual way and not through the growth, as might at first sight appear probable.

adults than in children. (6) There is no evidence for the view that infection takes place by way of the genital tract in the female,<sup>4</sup> nor that it occurs by direct spread through the diaphragm or from the gastro-intestinal tract. (7) Surgical treatment is inadequate as the first line of defence, and owing to the nature of the condition always will be, but it is indispensable in helping other methods. (8) Amongst the pathogenic organisms present in these cases there is some variety. Various strains of pneumococci typical in all respects, pneumococci showing some atypical features, or organisms which show some of the features of pneumococci and some of the features of streptococci. As, in some cases, the thoracic viscera show typical pneumococci and the abdominal show a mixed type, it seems possible that the latter represent 'altered' pneumococci, showing changes produced by the particular tissues in which they are growing; it is perhaps to this group that the '*Streptococcus intestinalis*' belongs; on the other hand, they may represent mixed infections, as some cases seem to be. There are no true streptococci in this series—to employ what would appear to be a necessary paradox.

#### *Frequency.*

The condition is rare in adults, but is probably more common than is usually supposed. In the records of 6,000 cases of pneumonia in adults investigated at the London Hospital it occurred in only one—a man aged 46 years; but two cases in adult females are known to me by report, one of the type of Group I and the other of Group III of clinical cases (see page 221), but they are not in the records. Of its frequency in adult females, as the result of infection of the genital tract, puerperal or other, no statement can be made. There is no case in this series. It has been stated already that this is a different clinical condition from the one under consideration. *In children.*—Compared with other varieties of general peritonitis in children its frequency is as follows: In 136 cases of general peritonitis due to various causes (the commonest being appendicitis and tuberculous infection) 37, or nearly a quarter, were pneumococcal, either certainly, as shown by bacteriological examination, or highly probably because of their clinical and morbid anatomical resemblance to the other cases. Another set of figures shows the following (here simple cases of

<sup>4</sup> The slightly greater frequency of pneumococcal peritonitis in the female (1.25 to 1.0 in this series in children) is explained by the facts (I quote these facts from Francis Warner, 'Constitutional Development and Social Progress of Boys and Girls from Infancy,' *Lancet*, London, 1907, ii)—(a) that after the first few months of life there are more girls than boys of the same age in existence, and (b) that though the percentage frequency of incidence of disease (including bacterial infections of various kinds) is proportionately greater in male children, the percentage of mortality of disease (including bacterial infections of various kinds) is higher in female children. That is to say, the power of resistance is lower in female than in male children. Therefore, given infection with the pneumococcus, in the female this will more often take a severe form, with such manifestations as peritonitis, than in the male, in whom the manifestations will more often take a relatively milder form, such as pneumonia alone.

appendicitis are excluded, and cases of all ages are taken together):—Total number of cases of general peritonitis, 554. Pneumococcal, 18, or about 1 in 31. But there is the constant difficulty and difference in personal equation, in deciding what constitutes 'general' peritonitis, and so the above figures cannot be very closely held to.

*Age and Sex Incidence.* All the cases in this series of 57 were under ten years of age. But there was an adult male aged 46 years, and there are two adult females known to me by report. There were, of five years of age and over, 19 cases or 33.3 per cent. (males 7, females 12), or (for this group over five and under ten years old) 36.84 per cent. males and 63.16 per cent. females. Of those under five years of age, 38 cases or 61.4 per cent. (males 18, females 20), or (for this group under five years old) 47.37 per cent. males and 52.63 per cent. females. Of those under two years of age, 21 cases or 36.8 per cent. (males 10, females 11), or 47.62 per cent. males and 52.38 per cent. females. Of those of one year or under, there were 9 cases or 15.7 per cent. (males 4, females 5), or 44.4 per cent. males and 55.5 per cent. females. The oldest case was aged 9 years, the youngest case 8 weeks. In the younger children the incidence of the disease is more equal in the sexes than in the older. Though girls are still the more often affected, this majority is smaller in the younger children.

### *Ætiology.*

*Predisposing Causes.* Defective hygiene, especially overcrowding, has considerable influence in producing all pneumococcal infections and therefore peritonitis. Overcrowding acts in more than one way. In the first place, it is obvious that if the pneumococcus is present in any individual of a number, either in the naso-pharynx or in the lungs, overcrowding will predispose to its conveyance to the naso-pharynx of other individuals. In the second place, combined as it usually is with defective sunlight, lack of fresh air and proper exercise, it tends to deterioration of the general health, to constant lowering of the general resistance. Vulnerability is thus increased.

In some of the cases there is a fairly recent history of measles, of whooping cough, or of epidemic enteritis. In two, chronic nephritis was present, whether as predisposing cause or as one of the effects of a general infection, or as an independent association, is uncertain. A previous attack of pneumonia had occurred in one case. This is uncommon, since these cases, apparently because they are very susceptible to pneumococcal infection, usually develop peritonitis in the first attack and die forthwith. (Whether such as recover from peritonitis subsequently become re-infected cannot be stated from this series.) Climate and season appear to have some influence, winter and spring months being much the commonest time of onset, as in all pneumococcal infections.

More important than these is, it seems, individual susceptibility, general and local. The factors concerned in any pneumococcal infection are, of course,

on the one hand the advent of the micro-organism, its degree of virulence and the dose, and on the other the degree of power of resistance or susceptibility of the individual. It is only the last that it is proposed to discuss here, the others are exciting causes. In the first place, as regards general susceptibility, if one may here review well-known facts, it is obvious that the susceptibility to any pneumococcal infection varies within very wide limits in different individuals. Many grow to old age without becoming infected. In some infection takes the outward form of an attack of pleurisy, which may be considered one of the slightest expressions of pneumococcal infection. In others it takes the form of an acute pneumonia. This, in the more susceptible, recurs time after time; in the most susceptible of all many other lesions occur as well—endocarditis, pericarditis, meningitis, arthritis, peritonitis, &c. Thus in the human subject there seems to be a variation in the liability to infection in different individuals, similar to that observed in different species of animals. When the enormous fatality of pneumococcal infections in children is considered, it seems clear that all adults are relatively insusceptible, or have been so in childhood, for they have survived against the pneumococcus in the struggle for existence. There are facts that show that it may be acquired later in life, e.g. the fact that many slum-dwellers, who must be in daily contact with the pneumococcus nearly all their lives, do not acquire infection until middle life, the occurrence of terminal pneumonia of alcoholism, diabetes, cancer, phthisis, &c. In these cases, however, there is for the most part a tangible cause for lowered resistance. It therefore appears that all these cases of pneumococcal peritonitis represent the type of high general susceptibility to pneumococcal infection. The peritoneum is nearly always infected in early life, and it is usually during the first and only infection, while other individuals living under identical circumstances not only do not get peritonitis, but many do not get pneumonia or other pneumococcal infection at all.

There seems to be also a local susceptibility, for the peritoneum is attacked in these cases, while it escapes in the majority, and not infrequently in cases where other serous membranes, such as meninges or joints, are involved.

*The exciting cause.* This is the advent of the pneumococcus, determined by its dose and virulence. It seems a reasonable hypothesis that these various manifestations of pneumococcal infections—pneumonia, arthritis, peritonitis, meningitis, bone lesions, &c.—are produced by different strains of pneumococci. And the experiments of Eyre have shown this to be the case in animals in the laboratory. The present series of cases proves that there is considerable variety in the characters shown by pneumococci occurring in pneumococcal peritonitis. These were the following:—Of twenty-four cases of peritonitis, which are here called pneumococcal peritonitis, the pneumococcus was present in peritoneal pus, in typical morphological and cultural form and pure culture, which grew readily, only thirteen times. In six of these it was also present in the heart's blood, spleen, and other serous spaces. In the other seven, cultures from these parts were not made, but only from peritoneal pus. In five other



cases the pneumococcus was morphologically typical and in pure growth in the peritoneal fluid, but was atypical in fermentation tests, resembling *Streptococcus pyogenes* in this respect. In two other cases the pneumococcus, present in pure culture in peritoneal pus, showed defective growth in sub-culture and died out. In one other case *Streptococcus pyogenes* was present with pneumococcus. In two other cases there was more than one other organism present, but the pneumococcus in much the greater number. In two other cases the peritoneal pus gave a pure culture of pneumococcus in typical form, but pericardial fluid gave apparently *Streptococcus pyogenes* in pure culture. (In these, however, it is uncertain whether these were really streptococci or only atypical pneumococci.) One case of the first series showed the presence in the peritoneal pus of a typical pneumococcus and an atypical one, on culture. A sub-culture grew only typical pneumococci, showing probably the conversion of the atypical into typical form. In one case a culture from an empyema showed typical pneumococci, that from the peritoneal pus showed an organism which was either an atypical pneumococcus or *Streptococcus pyogenes* or 'intestinalis'. In two other cases, not in the above twenty-four, there was a *probable* pneumococcal peritonitis associated with tuberculous peritonitis and tuberculous ulceration of the intestine.

There were many different strains of pneumococci in these cases, as shown by morphology, vitality on culture, and fermentation reactions. In some cases there seemed to be more than one organism present, commonly the *Streptococcus pyogenes* or 'intestinalis', as well as the pneumococcus, but it is more probable that this was really an atypical pneumococcus and not a streptococcus than that there was a double infection. In some cases accidental contamination occurred. It seems possible that in cases where the organism was atypical this abnormality may have been the effect of growth within the body, the result of action on the part of the tissues in which the organisms were growing; for it has been shown experimentally that atypical and typical pneumococci may be isolated from different lesions in the same case, and that the atypical can sometimes be converted into the typical by culture and animal inoculation. In the three cases in this series that recovered, the organism was atypical in two. It might be supposed that the cases in which peritonitis becomes localized are produced by one variety of pneumococcus, and the cases in which it remains generalized are produced by another. But there is no evidence for this. It seems rather to depend upon the factors of dose, virulence and power of reaction, general and local.

#### *Mode of Infection.*

The organism might conceivably reach the peritoneal cavity in several ways. Through the Fallopian tubes from the vagina in the female; through the intestinal walls, from the gastro-intestinal mucous membrane; from the arterial circulation, in a general septicaemia, by a process of embolism of bacteria; by

direct spread through the diaphragm (by continuity) from the pleura; from the pleura or mediastinum, by passage along the lymphatic channels to the peritoneum. If infection comes from the general circulation, the organism may have reached the blood-stream in several ways:—By way of the lungs. In this case, if pneumonia is present, it is a primary focus of disease, and corresponds to the local lesion of animal inoculation. Through the bronchial and mediastinal lymphatic glands and lymphatic channels. Pneumonia and pleurisy, if present, are here secondary metastatic effects at a place of lowered resistance (just as the peritonitis is), or a focus produced by direct spread from these glands. By way of the mesenteric lymphatic glands, from the gastro-intestinal mucous membrane. It might then infect the thoracic lymphatic glands (with resulting changes as before) or the general circulation by way of the thoracic duct. From the gastro-intestinal tract direct; from some extraneous focus such as an inflamed tonsil, naso-pharynx, &c.

Infection from the genital tract cannot occur in males, which in this series were nearly half the cases (proportion of males to females was as 1.0 is to 1.25), yet the clinical and post-mortem features of cases are broadly the same in the two sexes. In no case in this series was there any evidence of infection by this route. The condition seems to have been confused with pyosalpinx or perimetritis (in which the pneumococcus has been found), but this symptom complex and pyosalpinx afford quite different clinical pictures, and pyosalpinx does not occur in the male. The presence of vaginal discharge in such cases is of no significance. It is the exception, not the rule; it occurs quite commonly in otherwise healthy children; in the only case in this series in which there was a vaginal discharge this can be shown to have come down from the abdomen, and was thus an effect, not a cause, of peritonitis.

The argument for the view that infection is from the gastro-intestinal tract seems to be the following (6):—‘Pneumococci have repeatedly been isolated from the intestinal contents, and have been demonstrated passing through the necrosed Peyer’s patches of a case of gastro-enteritis, and lying beneath the peritoneal coat, and even in the coats of lymph exuded on the surface of the bowel. The well-known fact that the wall of the bowel may, as the result of some slight lesion, allow organisms to pass through it, taken along with the clinical fact that diarrhoea is often the initial symptom of pneumococcal peritonitis, points to the intestine as the most probable source of the infection.’ The following considerations seem to show the incorrectness of this view: it is obvious that the pneumococcus may have reached any of the above situations from the arterial circulation; and this seems more probable than that it came from the enteron. The pneumococcus has been isolated in individuals dying as the result of trauma, &c., showing no symptoms or signs of disease; from the naso-pharynx, mouth, liver, bile-tracts, spleen, tubules of the kidney, bladder, urethra, vagina; from the urine (from almost every organ in the body; these organs being otherwise normal). Therefore the mere presence of the pneumococcus in the gastro-intestinal tract does not prove pathogenicity (13). There-

fore, and in view of the large variety of other organisms which harbour in the intestinal tract, and commonly produce that condition, in the cases of gastro-enteritis stated the pneumococcus may not have been the pathogenic agent. The fact that in pneumococcal peritonitis the organism has been found in the flakes of coagulated lymph on the serous coat of the intestines does not prove that it comes from the enteron; for it seems equally probable that it came there from the arterial blood-stream, as it presumably does in pleurisy; nor does the presence of the organism in the subserous tissue prove this point, since it may, with as much probability, have come from within the capillaries. The tissue fluid in which it lies, whether a simple serous fluid or an inflammatory exudate, has admittedly arisen from there by osmosis. The organism probably accompanied this. It is admitted that in cases of gastro-enteritis the excess of fluid in the enteric contents is derived, by osmosis, from the capillary circulation, passing through the mucous membrane into the intestinal canal. If pneumococci are present in the intestinal contents in pneumococcal peritonitis they may have had the same origin. The mucous membrane of the gastro-intestinal tract is almost or quite impenetrable to this organism unless it is injured or necrosed, when it becomes less so (13). If either of those conditions of the mucous membrane occurred in pneumococcal peritonitis, infection by this route might be supposed to occur. But in only two cases in this series of fifty-seven was there any necrosis of the mucous membrane (namely tuberculous ulceration), and here both forms of peritonitis (tuberculous and pneumococcal) were present. Jensen in 1903, in an analysis of 106 Continental cases, i.e. all those hitherto published, noted, amongst those of all kinds, the following:—Perforated gastric ulcer four times, cicatrix of the lesser curvature of the stomach once, ulceration of stomach other than the above, five cases (Weichselbaum and Banti), in two of which this was carcinomatous, tuberculous ulceration of lower ileum one case, catarrhal colitis one case, membranous enteritis one case; in one case there was 'multiple ulceration of the caecum, transverse and descending colon, the mucous membrane of the small intestine being normal. The ulcers had clear-cut margins, not undermined, and were of the area of millet seed. The muscular coat as far as the serosa was involved.' 'Microscopical examination showed the presence of diplococci throughout the whole thickness of the intestinal walls,' and, it is added, 'In this case the pneumococcal infection was complicated by typhoid fever.' Flexner observed 'dysentery diphtherica' in one case and 'entero-colitis' in another. Lennander found 'follicular enteritis and appendicitis' in one case and 'catarrhal appendicitis' in another; in a third there were 'multiple ulcerations of the mucous membrane at the lesser curvature of the stomach the size of a grain of rice or smaller; the appendix showed ulceration of mucous membrane at its distal end; there were submucous haematomata in the upper ileum, and in the lower ileum acute enteritis'. Ménétrier and Legroux record, in one case, swelling and oedema of the intestinal walls with pneumococci throughout their thickness. In all the other cases quoted by Jensen the mucous membrane of the stomach and intestines was normal on post-mortem examination. That is to say, the mucous

membrane of stomach or intestines showed changes in only 20 out of 106 cases. These 20 showed much diversity in the morbid anatomy of the gastro-intestinal tract. In some the condition associated seems to be clearly 'accidental' (e. g. perforated gastric ulcer, cicatrix of an old simple ulcer, carcinoma, tuberculous ulceration, typhoid ulceration), and of the other conditions they may, for the most part, quite as well be effects of septicaemia or mere associations as accessory causes of peritonitis. If infection occurs commonly by the route of the gastro-intestinal tract, more frequent and more constant necrotic changes than are shown in the above might be expected. Dieulafoy has described two, Marchisio four, and there is one case in the *Bulletin de la Société anatomique*, June, 1899, in which pneumonia, general peritonitis, and multiple haemorrhagic ulceration of the gastric mucosa occurred in adults. There are a good many other somewhat similar cases in the literature. Dieulafoy's cases showed multiple lesions, from all of which the pneumococcus was cultivated post mortem. Swallowed sputum will account for the gastric ulceration here, but embolism (of bacteria) seems as likely; and if the hypothesis that the peritoneum became infected from the arterial circulation is not proved by these cases; neither is it proved that infection took place through ulceration, for in the vast majority of cases, otherwise precisely similar, there is no ulceration; infection occurs by some other route, and this is also possible here. In pneumococcal peritonitis the mesenteric glands are usually normal; the bronchial glands are always inflamed. This is not compatible with infection from the intestinal tract. In all other conditions in which infection arises from that tract the mesenteric glands are constantly affected. Further, experiments with regard to pneumococcal infection in lower animals show that the glands draining the focus of inoculation are always affected (13). These facts exclude the possibility of infection from the gastro-intestinal tract, and point to its occurrence through the respiratory tract. In most cases of pneumococcal peritonitis the mucous membrane is normal throughout. In a few there is congestion of mucous membrane, usually local, occasionally in patches, very rarely general, in the small intestine. Occasionally Peyer's glands are enlarged, usually quite locally. In the large intestine the mucous membrane is uniformly normal. Such changes might with as much probability be produced by a cause acting from within the capillary walls as from without them, e. g. by toxæmia or septicaemia, as by organisms acting upon the mucous membrane from the lumen of the intestine. And the same is true of the symptoms vomiting and diarrhoea, which may be the result of toxins secreted by reversed osmosis as they are in septicaemic and pyæmic conditions produced by other organisms (e. g. staphylococcus).

It is sometimes stated that diarrhoea is the first symptom observed. This is unusual; more frequently pain and vomiting precede it. Pain is usually the first symptom. Diarrhoea and vomiting are regarded as evidence of gastro-enteritis. Pain is presumptive evidence that the peritoneum is inflamed. If this inflammation takes origin from gastro-enteritis, one would expect the latter to precede pain for some time, in order to permit the organism to make its way

to the peritoneum from the lumen of the intestine. As a matter of fact, it does not do so. When diarrhoea is the first symptom, it is followed almost at once by pain, at a period, one would suppose, too short for this migration to have occurred. This tends to show that peritonitis precedes gastro-enteritis, and that the latter is an effect (by toxic products), and not a cause, of peritonitis. Diarrhoea and vomiting, probably the effects of toxæmia, occur in all kinds of peritonitis of whatever origin, unless the muscular wall of the intestine is paralysed, so that it is unnecessary to look upon gastro-enteritis as a cause here. (In pneumococcal peritonitis the intestinal muscular wall is not paralysed.)

In any case of peritonitis, of whatever kind, infection of the peritoneum, whatever its origin may be, must be either local or general at first. In pneumococcal peritonitis the condition is, clinically, *general* at first, and on operation or autopsy no local focus of origin is found. By analogy with other known conditions (if the method is to be trusted) there are only two ways in which this can be explained, i. e. either by infection by the arterial circulation, or perhaps, in addition, by the lymphatic system. (An analogous condition seems to be the variety of tuberculous peritonitis that occurs without tuberculous ulcerative enteritis.)

In certain cases infection cannot arise from the enteron, but may arise from the general circulation. In one case the pus was found on operation to be situated extraperitoneally in the subserous tissues behind the lower part of the anterior abdominal wall. In another case, after broncho-pneumonia (following measles) some three to four weeks previously, a tense swelling suddenly appeared in the right scrotum; it was irreducible and without impulse on coughing. There was no vomiting or diarrhoea or other evidence of gastro-intestinal disturbance, and the bowels were open. This proved at operation to be an old hernial sac; it contained no intestine or omentum, the neck was made out to be nearly obliterated, and, as there was no impulse on coughing, it was shut off from the general peritoneal cavity. The sero-fibrinous fluid in this old sac contained the pneumococcus in pure culture. In these cases the only possible source of infection seems to be the general circulation.

The reasons already given against infection by other routes seem by exclusion to make infection by the circulation likely. Experimental medicine teaches that cases of 'pneumonia' are really septicaemic conditions; the arterial circulation is therefore, *a priori*, the most probable route of infection of the peritoneum. Other conditions, such as meningitis or arthritis, sometimes precede peritonitis. In such cases there must have been general septicaemia before peritonitis developed. The anatomical distribution of the arteries, rami intestini tenues, and arterioles of the intestines and subperitoneal tissues of the abdominal walls would favour the infection of all parts of the peritoneum simultaneously. Clinical observation shows that this is what occurs, peritonitis being general at first. This is incompatible with infection by other routes, which would all tend to make it local at first. When infection can be proved to occur by other

routes it is local. (For example, pneumococcal perigastric or subphrenic abscess after perforated or 'leaking' gastric ulcer.) Other peripheral structures are not infrequently infected by the pneumococcus, for instance, the periosteum, epiphyses and medulla of bones, and the subcutaneous tissues. Here infection occurs by way of the arterial circulation, of necessity. Lymphatic glands, e. g. cervical, inguinal, and femoral, are sometimes in a condition of acute adenitis in cases of pneumococcal peritonitis, as in several cases in this series. This was sometimes suppurative, and the pus had the characters of pneumococcal pus (the bacteriology of these particular cases is, however, not certain). If the lymphatic system is concerned in the return circulation from terminal capillaries the only means by which these glands became infected is via the capillaries, through the arterial circulation, in a general septicaemia. They cannot have become infected through the lymphatic system alone. Other serous cavities are frequently infected. In them infection can only have occurred from the general circulation; for example, the endocardium, subarachnoid space, synovial cavity of joints, bursae, and lymphatic cysts such as cystic hygroma. It is more probable that the route of infection that has been followed in all these serous cavities is also the one in case of the peritoneum (its accidental proximity to the enteron notwithstanding) than that a new method occurs for this alone. When several of these are inflamed together, the general circulation is the only connecting link between them all. Any or all of these may be associated with peritonitis. Peritonitis occurs in other septicaemic conditions, where all sources of infection other than the general circulation can be excluded.

The evidence that infection takes place by direct spread through the diaphragm is inadequate. The fact that collections of pus sometimes occur in the subdiaphragmatic region with pneumonia or empyema seems to be all there is. Two such cases in this series are referred to, but they have a different explanation as to their origin. Infection of the pleura and lung from the abdomen is fairly common, but that the converse occurs seems by no means certain. The anatomical arrangement of the lymphatics passing from peritoneum to thoracic serous spaces, the direction of the lymph-flow, and the negative pressure developed within the thorax would seem to favour, with the lymph-flow, the spread of infection from peritoneum to pleura, but to act against it in the opposite direction. The peritoneal cavity specially favours localization, by adhesion-formation, matting of omentum, &c.; therefore, inflammation spreading from thorax to abdomen would tend to become localized in the upper abdomen, and only become general subsequently, if at all. The two cases quoted above, however, show that the converse had occurred. Another case illustrating this point was one in which an empyema necessitatis of several weeks' duration had pointed through the chest wall in two places; there was no peritonitis. This would seem to be the sort of case in which, if ever, infection of the peritoneum through the diaphragm should occur. During resection of a rib a hole was made through the diaphragm. Six weeks later there was an abscess in the upper abdomen, pointing at the umbilicus; this was drained. At autopsy it

proved entirely shut off from the rest of the peritoneal cavity (which was normal), and it communicated directly with the empyema cavity. In this case infection through the diaphragm only occurred when there was an anatomical defect such as the above (or ulceration would doubtless represent the same condition). There is, however, no evidence that simple ulceration downwards ever occurs. The occurrence of empyema necessitatis, always of long standing, is against it; this follows the line of least resistance; the upper surface of the diaphragm offers a stronger resistance to ulceration than the chest wall because its contraction (away from an empyema) is more powerful than that of the chest wall; its upper surface is convex in contraction and relaxation, while that of the chest wall is concave. The mechanical effect is concentration of forces against the chest wall and their diffusion in the case of the upper surface of the diaphragm. (In a similar way ulceration of the diaphragm from below is favoured mechanically, and infection of the pleura from subdiaphragmatic collections readily occurs.) It seems unlikely that infection ever arises in this way, for in fifty-seven cases some evidence of this having occurred should be forthcoming. There is none.

Infection appears to occur in part through the lymphatic channels. The bronchial glands show acute adenitis. There is anatomical and physiological continuity of the serous spaces (pleurae, pericardium, and peritoneum) with these. The frequency with which all are inflamed together in pneumococcal 'peritonitis' seems suggestive. From experiments upon animals it seems probable that the pneumococcus may gain entrance to the body by way of the bronchial lymphatics. If this is so, inflammation of the bronchial glands may of course occur as the first step towards infection of the general circulation, or of serous spaces and mesenteric glands. On the other hand, it would seem that it may be the effect, either of general septicaemia (since it occurs in nearly all septicaemic conditions), or of inflammation of the serous spaces. The significance of these morbid-anatomical facts seems uncertain.

Though infection probably reaches the circulation from some part of the respiratory tract, there is a possibility of its arising from extraneous foci. In three cases in this series, and in a published case, there was acute tonsillitis, but no bacteriological examination of the tonsillar exudate was made in any of them. If the organism had been found there, however, this would of course not have afforded any proof that infection occurred through the tonsil, since the pneumococcus may not have been acting as a pathogenic agent, or only as a local one. This is shown by the frequency with which it is found in the naso-pharynx of healthy individuals. A sidelight is thrown upon this aspect of the subject by a case described by Rabot, of Lyons, of pseudo-membranous angina of pneumococcal origin. Stress is laid upon the absence of severe constitutional symptoms in this condition. It did *not* produce septicaemia. A similar case, Peltsohn's, is quoted. Cases of Chareau and of Gloves are also quoted, but in the first death was from meningitis, and in the second from pseudo-membranous bronchitis and pulmonary disease. The point, therefore,

remains undetermined, though in both these it is probable that the general infection occurred through the respiratory tract. Many of the cases in this series showed the presence of pneumococcal pus or turbid fluid in the middle ear, post mortem. It seems probable, however, that this is an effect of septicaemia rather than a cause of it. It usually occurred in cases in which there was a very severe infection with multiple local lesions; it rarely gave rise to any symptoms during life; and the tympanic membrane was always intact. It was sometimes probably an early post-mortem change. That it ever acted as a focus of infection is unlikely, for there was a total absence of sinus or jugular thrombosis, or other changes such as usually precede septicaemia arising from inflammation of the middle ear. There are other facts which tend to show that when the pneumococcus produces inflammation in extraneous foci it does not produce general septicaemic infection. Such are, for example, cases of cellulitis, prostatitis, and urethritis recorded in the literature, and the cases of pyosalpinx in adults.

### *Morbid Anatomy.*

With the exception of changes in their serous coats the viscera are usually normal. When other changes are present they are those of any septicaemic conditions, but as such are relatively slight. The *liver*, except for perihepatitis (which is always present), is usually normal. Occasionally it is enlarged. In a few cases its substance has undergone fatty changes. Rarely the organ is congested. This change, though usually general when present, may be quite local. In two cases the liver substance showed cloudy swelling, in one a few patches of necrosis. In two it was softer than normal. And these were all the changes shown in the series of fifty-seven. Changes are therefore uncommon, and not very marked when present. The *spleen*, though usually normal, except for perisplenitis, may show morbid changes. In some cases, where the infection is a particularly severe one, the spleen is enlarged and congested; its substance may even show haemorrhagic areas. In some cases of this kind it is softer than normal, or it may be diffuent. This diffuence may be confined to the central portion or may be general. In these cases there are, for the most part, but not invariably, associated changes in the liver and kidneys, such as enlargement, congestion, or even cloudy swelling of moderate degree. In these cases the latter condition is sometimes associated with marked injection of vessels or haemorrhages in the subserous tissues. Rarely there is hyperplasia of the spleen pulp, probably an accidental association. The *kidneys* are nearly always normal. But in the more severe cases, associated with changes in the liver and spleen, they may be enlarged and congested, or show cloudy swelling of moderate degree. In two cases there was a condition of chronic parenchymatous nephritis, whether as a predisposing cause of the infection, as accidental association, or one of the effects of the general infection, is uncertain. In no case was there amyloid change in any of the viscera. The *Fallopian tubes*, *uterus*, and *ovaries* were normal in all female cases but one, except for the fimbriae and



serous coats. These showed in all cases the same changes as the rest of the peritoneum. In the one case referred to, the tubes were not enlarged and their mucous membrane was not inflamed, but pus could be expressed from both. The endometrium was somewhat congested; but the uterus contained no pus. The vagina contained pneumococcal pus, but was not inflamed. It seems clear that the vaginal pus came down from above. (See Mode of Infection.) In no case was there any evidence that infection of the peritoneum occurred through the genital tract in the female. The chief, and usually the only change observed in the *stomach and intestines* was in the peritoneal coats. The peritoneum presents the appearances usual in acute inflammation. There is also a coating of shaggy coagulated fibrin or pyolymph as a rule; this may simply stick the coils together, or there may be true adhesions, either general or local. (The condition present, of course, depends, to a large extent, upon duration and the amount of resistance to bacterial invasion that has been exhibited, of which pus formation and the extent of adhesion formation, when present, afford some sort of rough estimate.) In rare cases there is no lack of gloss, but simply pus in thin films between the coils, which are not adherent. (These seem to represent mild infections occurring in cases when the resistance is very low.) The subperitoneal vessels and rami intestini tenues are injected in many cases but not in all. In the most severe there are small petechial subserous haemorrhages throughout the peritoneum. The peritoneum is in the same condition throughout, except with regard to adhesions, which, when present, may be local, or more or less general (according to duration and the degree of resistance that has been exhibited in life). The small intestine is hardly ever distended, showing that the muscular wall is not paralysed. In two cases, however, some distension was present. The large intestine is not distended. This absence of paralysis of the intestinal muscles seems partly to explain the presence of diarrhoea, rather than of constipation in this condition. The mucous membrane of the stomach and intestines is nearly always normal. In one case, however, that of the small intestine was congested throughout. In five cases there were patches of congestion, in three small and local, in two generalized. In one case there were a few small patches of submucous haemorrhage. In three cases Peyer's patches and the follicles were enlarged throughout, but there was no congestion of the mucous membrane. In none was there any necrosis or ulceration, save in the two cases accidentally associated with tuberculous enteritis and peritonitis. The mucous membrane of the large intestine is practically always normal also. In one case there was an ulcer of the mucous membrane of the colon of uncertain nature. In another the mucous membrane was thickened and somewhat congested. (In another, though the mucous membrane was normal, the muscular wall was somewhat oedematous.) The appendix was normal in every case. The *mesenteric glands* are usually normal, but in three cases they were congested and enlarged. In nine others there was enlargement but no congestion. In one case of the above the retro-peritoneal as well as the mesenteric glands were enlarged and congested. The

fact that these glands are usually normal seems incompatible with infection from the enteron. It seems more probable that the condition of the mucous membrane and of the mesenteric glands, when either are inflamed, are both the effects of septicaemia or of peritonitis than that they stand in the relation of cause and effect to one another. It does not seem likely that either plays any part in the causation of peritonitis, because changes in them are the exception and not the rule. Such changes are therefore probably effects rather than *causes* of peritonitis. *Lungs.* Lung disease was present in all cases post mortem. In forty-one cases there was *clinical* evidence of lung disease, either empyema, pleurisy, or pneumonia. In fourteen cases there were no signs discovered during life. In all of these that came to autopsy but two, there was pneumonia or traces of its remains in adhesions, &c. In these two there was congestion and oedema of part of both lungs with a small collection of sero-fibrinous fluid in the pleurae at the bases. The *bronchial glands* are always enlarged and congested; there is adenitis more or less acute; sometimes this is suppurative. In one case all the mediastinal glands were in the latter condition.

### *Symptoms and Signs.*

The clinical picture of this condition is clearly defined. It is one of general peritonitis, of abrupt onset, usually preceded by, occasionally accompanied by, but in rare cases followed by, a pulmonary lesion. Other lesions besides those of the peritoneum and lung or pleura are not infrequently present, such as meningitis, pericarditis, arthritis, &c. Thus, the peritoneal condition only forms part of a symptom complex of acute abdominal and acute thoracic disease, not always synchronous in time of onset and often combined, as above, with other lesions. A case will generally show the following features:—

*Onset.* After a period varying from a few hours to one or more weeks, during which symptoms and signs of an acute pneumonia or pleurisy are the prominent feature, or have been for part of that time, the abdominal condition sets in abruptly, with severe abdominal pain, followed by vomiting and diarrhoea. There is high fever, the temperature rising to 103° or 104°, and weak, very rapid pulse. The tongue is furred, the breath foul. There are sordes on the lips. The face is pale and sweating, the eyes sunken, the corneae and conjunctivae hazy. This 'facies abdominalis' early becomes marked. The alae nasi may be working, or there may be herpes facialis. Cyanosis and dyspnoea may be present. Anorexia is complete. In older children and adults severe headache is commonly complained of. The central nervous system is intoxicated, there is somnolence, drowsiness, restlessness, delirium. Sometimes general tremors are present. Myotatic irritability is sometimes present at this stage, but usually only later. With this condition signs of pneumonia are usually present; in some cases there is a history of it within a recent period (up to four weeks), in a few it only appears later on. The vomit shows nothing characteristic, but is occasionally blood-stained or contains altered blood. The stools are very loose, foul and

greenish or yellow, occasionally jelly-like mucoids, sometimes blood-stained. Rarely, the initial diarrhoea is of almost pure blood. Tenesmus and dysuria are occasional. The abdominal pain is nearly always general from the first. Occasionally it may be localized for a time. These sites, if present, are eccentric and do not correspond to the usual sites of pain of acute abdominal conditions, such as renal, hepatic, or appendicular colic. The pain is usually continuous and not paroxysmal, but was in one case periodic, coming on at about the same time night and morning, and enduring for a few hours at a time. Physical examination at this stage reveals no distension of the abdomen. It is usually retracted. Movement is defective or entirely absent. There is no local bulging. The superficial tenderness soon becomes very acute over part and then the whole of the abdominal area. It is general from the outset or very early becomes so. Where palpation can be performed, deep tenderness seems to be general also. The abdomen is resonant all over, or there are at this stage doubtful signs of fluid in the flanks. Rectal examination at this stage reveals no bulging of Douglas's pouch, but tenderness is usually marked. Leucocytosis, of neutrophilic polymorphonuclear type, with marked fibrin network, is present. In a few cases, which, however, seem to be commoner in adults than in children, there is collapse at the onset. If such come under observation at this stage, the resemblance to a perforation of enteric fever or ruptured viscus due to other cause may be strong. In such the history and signs of disease other than abdominal are of course all-important.

*When the effusion has appeared.* After a period varying from a few hours to a day or so abdominal distension and definite signs of fluid in the flanks appear. As a rule they soon become those of a general effusion. Rectal examination now reveals a bulging of Douglas's pouch, or a tense swelling there. The leucocytosis has increased. Abdominal rigidity now begins to pass off and the abdomen gradually becomes tumid. The acuteness of the superficial tenderness, though it may persist for days, usually diminishes, its area gradually lessens, and from now on slowly disappears. In the severest cases, those with the highest temperature, the most rapid and feeble pulse, and all the general indications of a very severe intoxication, the severe symptoms of the onset persist without abatement until death, which usually occurs in a few hours. It may occur almost before there are definite signs of effusion. In most cases, however, with the onset of the effusion the severity of the condition moderates somewhat. The temperature falls a degree or so, the pulse becomes less rapid, the 'abdominal faeces' becomes less marked or disappears. The pain becomes less severe and commonly dies away. Vomiting becomes less urgent or ceases. Diarrhoea, though it often continues for days, or even weeks, usually ceases also. All the symptoms of intoxication become less marked, and the patient now begins to present an appearance of relative comfort compared with that of general peritonitis due to other causes. Rigidity and tenderness, superficial and deep, diminish and die away.

*Subsequently.* From now on the condition in many cases becomes subacute,

with hectic fever or without it. It may even verge upon the chronic. (A case has been more than once mistaken for ascites.) The colour often becomes good. Rapid emaciation occurs. This is especially marked in the limbs. The collection of fluid in the abdomen may remain general, or may become localized, and either condition may persist for weeks. When this occurs the condition is often mistaken for tuberculous peritonitis, particularly when lung signs have persisted. The localized collections are usually mistaken for appendix abscess. The liver and spleen are now sometimes enlarged, but there is no albuminuria. The collections of fluid, both local and general, have been known to point at the umbilicus and burst there. They sometimes undergo absorption.

The above picture of the onset represents a severe case. In many the symptoms and signs are not so severe, and the toxæmia is less marked. Though, as a rule, lung trouble precedes the abdominal condition, it may come on synchronously with it or may follow it. There may be a latent period of apparent health or convalescence between the two conditions, due, no doubt, to the well-known occasional latency of pneumococcal septicaemia. The abrupt onset of peritonitis described above is not invariable. It is sometimes insidious, apparently without pain or tenderness, and shows itself by gradual swelling of the abdomen. This may be so slight as to escape observation, and the condition may only be discovered post mortem. With regard to the symptoms of onset—abdominal pain, vomiting, and diarrhoea—the first is usually abdominal pain, followed first by vomiting and subsequently by diarrhoea; in a good many cases vomiting, and in some both vomiting and diarrhoea, precede the onset of pain; in a few diarrhoea is the first symptom. There may apparently be no pain, but this is unusual; such cases are those of quite young children, unable to express their feelings, and therefore the presence or absence of this symptom can only be inferred. Occasionally there is no vomiting. When present it usually passes off in a few hours, but may be repeated at intervals of a day or more. Diarrhoea is almost invariably present. It is sometimes stated to be usually the first symptom. This is not the rule in this series of cases. Though very rarely there is no gastro-intestinal disturbance or even constipation at the onset, this is soon followed by diarrhoea, which, in this condition, is almost invariable. The whole infection, from the time of onset of pneumonia, may last for as much as three months; after the onset of peritonitis it may endure for weeks at a time; but death often occurs within a few hours of the first symptom.

Cases may be placed, from the practical standpoint, (such as, for instance, that of the out-patient room of a hospital, when they commonly first come under observation), in four groups. In Group I, on first observation, the case presents itself in the form of 'an acute abdomen'. The abdominal features stand in the foreground of the picture. It is probably from such cases as these that the term 'primary' pneumococcal peritonitis has arisen. These constitute about one-third of the number in children. In Group II cases show the same features but have some peculiarities of their own at the onset. For the most part swelling is the first thing noted. This is, to some extent, due to the fact

that they are younger children than the others, unable to express their feelings with regard to pain, &c., and it has not been noted that they were ill until swelling was observed by the mother. These constitute about one-eighth of the number in children. In Group III there are at the first observation both thoracic and abdominal features. These cases constitute about one-fifth of the number in children. In Group IV the features are those of thoracic disease at the time of first observation. In some, signs of peritonitis are subsequently observed during life; in others, because its onset is insidious, or more often because the abdomen is not examined, the condition is only discovered post mortem. The cases of this group constitute one-third of those in children.

*Distribution and characters of inflammation and exudate.* From this series of cases it seems probable that the peritonitis is at first always general. In cases that came to autopsy (i.e. 88.8 per cent.) there was evidence of

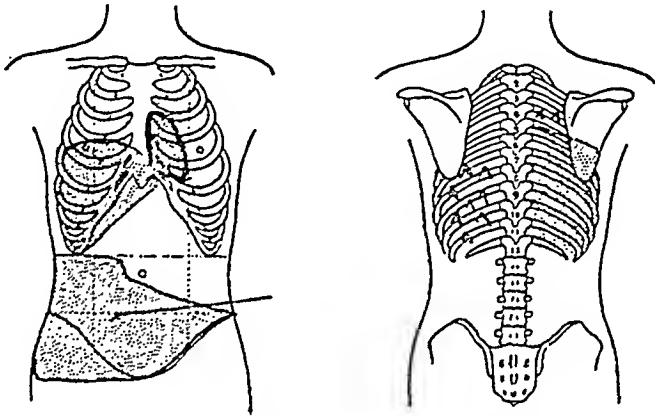


FIG. 1. V. D., aged 9 years, ill one day. On the right side of the chest in front, there was dullness, diminished air entry, tubular breath-sounds in places, increased vocal resonance, increased vocal fremitus, and no crepitations. The abdomen was retracted but moved well; the rectus stood out prominently; it was rigid everywhere, but more so on the right side; resonant everywhere. Behind on the left side a few scattered crepitations; on the right side dullness, tubular breath-sounds, increased vocal resonance, and fremitus, a few crepitations above but none below. The shading over the abdomen is the area of superficial tenderness.

general peritonitis in every one, either in the form of a generalized inflammatory effusion, or a local one, shut off by adhesions, with adhesions throughout the rest of the peritoneal cavity, showing that the inflammation, at first general, had subsequently become localized. In cases that recovered, of which there were 6 of 54 or 21.2 per cent., at the operation a local collection of fluid was found. In some of these there were generalized adhesions throughout the rest of the peritoneal cavity, showing that the peritonitis had at first been general. In the others that recovered this point was not made certain because the laparotomy went no further than simple incision and drainage; but from their resemblance in history, clinical course, symptoms, and signs to the last group it is practically certain that this is true of them also.

The case shown in Figs. 1-6 appears to illustrate the condition from the onset until localization occurs. In another case, aged 6 months, operated upon

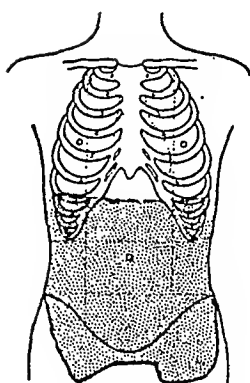


FIG. 2. V. D., aged 9 years, ill 4 days. It shows the area of superficial tenderness. The abdomen moved badly and was slightly distended, the veins were a little engorged, especially on the right side; no palpation was possible and there was no dullness.

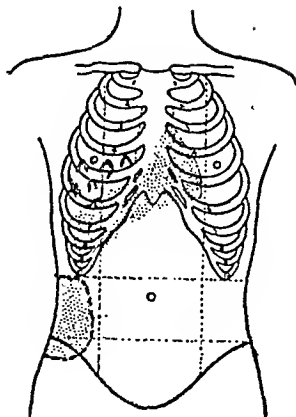


FIG. 3. V. D., aged 9 years, ill 11 days. On the right side of the chest the percussion note was diminished, the breath sounds were loud, the vocal resonance was slightly increased; a loud dry rub at the anterior axillary border. The apex beat was well within the nipple line and the heart was not displaced. The shaded area was very tender. There was no dullness in the loin.

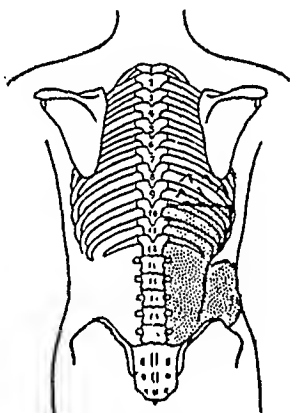


FIG. 4. V. D., aged 9 years, ill 13 days. There were fine pleural crepitations on the right side of the chest. The shaded area shows the superficial tenderness; no dullness was present, there was deep tenderness under the right margin of the ribs.

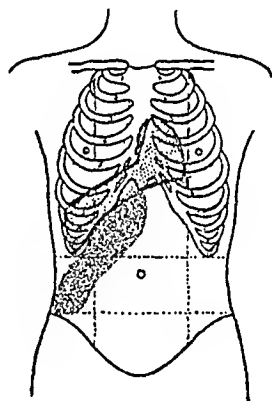


FIG. 5. V. D., aged 9 years, ill 16 days. There were no physical signs in the chest. Pain was marked in the right lumbar region and there was a hard lump in the abdomen. Shaded area as in other figures.

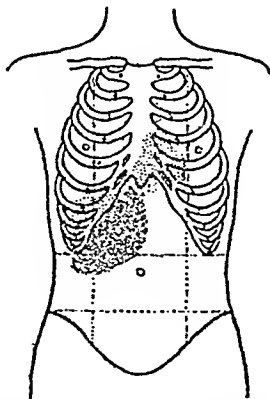


FIG. 6. V. D., aged 9 years, ill 17 days. The shaded area indicates superficial tenderness; under this there was a lump.

on the fifteenth day of illness, median laparotomy being performed, there was an abscess in the same situation and the intestines were marked by adhesions throughout. Death followed, but there was no autopsy. It, however, illustrates this point. Both these were males.

The case shown in Figs. 7 and 8 also illustrates this point. The diagrams show the diminution in the area of dullness that occurred in two days. As the first represents a duration of twenty-one days it seems clear that the peritonitis must have been originally general. But at the time of operation the abscess was local. In another case, aged 7 years, ill fourteen days, a similar condition was shown, 36 ounces of pus being evacuated from what, from the physical

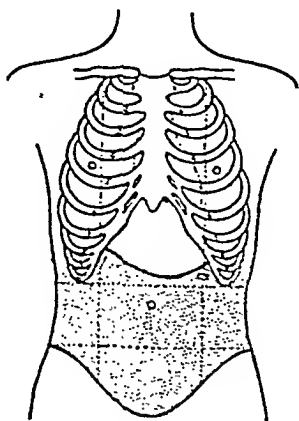


FIG. 7.

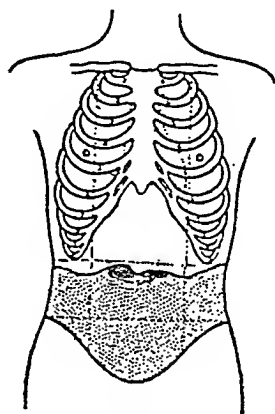


FIG. 8.

signs, was a 'local' condition. The abdomen, closed without drainage after evacuation of the abscess, refilled. Both these were females.

Another case, in a girl aged 7 years, both before and at the time of operation, was regarded as a local collection in the appendix region. Autopsy showed it to be general (and there were fairly recent adhesions in both pleurae, though there had been no signs in the chest during life). In another girl, aged 2 years 2 months, ill for several weeks, there was what was, considering the age of the child, an enormous abscess in the appendix region containing 8 ounces of pus, which, in view of the similarity to the other cases, seems suggestive, but as recovery ensued it cannot be definitely proved that this was originally general. In three other cases in girls aged 4 years, 1 year 6 months, and 11 months respectively, each with a history of several weeks' illness, there were local collections in the pelvis. In the two that died there were on autopsy generalized adhesions; in the other, recovery ensued and the point cannot be settled. In another case, in a girl aged 9 years, ill one day, the signs were compatible with a local collection, but on operation peritonitis was found to be general. Death occurred on the third day. The above are all the cases in this series in which the condition had any appearance of being local. Of those that died it would have been said, had they recovered, and had operation gone no further than the usual incision and drainage, that the

condition was local. But autopsy showed it to have been originally general; and it seems a fair inference that in the few where the point cannot be settled the same process has been going on, as they are so like the others. All these 'local' collections seem to be the remains of a peritonitis originally general or 'diffuse'. The following cases in the literature support this view. Walther describes a case with 'a very large abscess', which subsequently divided into two; one abscess occurring about the umbilicus, and the other in the region of the spleen. Gaillard describes a similar occurrence, one being found between the liver and diaphragm, and the other at the spleen, these having been originally one abscess. Sevestré describes a similar occurrence; one abscess was in the lesser sac and the other at the caecum.

Local collections may, it appears, be found anywhere within the abdomen; but they seem to occur more commonly in some places than in others. These are low-lying fossae in the recumbent posture. They do not correspond to any diseased focus of origin that can be found. There seem to be two factors at work here: first, the influence of gravity, and secondly, the matting and adhesions produced by the great omentum (and perhaps the mesentery). In this series there were: in subhepatic pouch, 2; in right iliac fossa, 2; in left iliac fossa, 1; in pelvis or lower abdomen, 3.

The view has been expressed in the literature that collections are found more commonly on the left side than the right (2). This was not observed in this series. It has also been stated that they occur commonly about the umbilicus. This occurred in this series in two cases, in which there were general collections of fluid associated with matting of omentum and intestines, the condition being more advanced in this region than elsewhere. Collections between the umbilicus and the symphysis pubis occurred in two cases. In three cases the fluid pointed at the umbilicus; in one of these it had ruptured there. This, which is said to be a common feature, only seems to signify length of standing of a collection of purulent fluid capable of producing ulceration. Such cases have lasted for a considerably longer period than is usual in general peritonitis caused by other pyogenic organisms. The condition is, of course, seen fairly frequently in tuberculous peritonitis, and one has seen it in a case of suppurating hydatid cysts of long standing. In one case of this series the pus was extraperitoneal.

*Characters of the exudate.* The characters of pneumococcal effusions, whether sero-fibrinous, sero-purulent, fibrino-purulent, or purulent, are so well known that it is enough to say that to judge by this series those occurring in the peritoneal cavity do not differ from those in other regions except very occasionally. In the 'local' collections the fluid is purulent. In the other cases it is, according to length of standing, fibrinous, sero-fibrinous, sero- or fibrino-purulent, or purulent. The well-known characters of pneumococcal pus, greenish, watery, flocculent, and inodorous, are in rare cases varied, but only in a very small minority. The variations are those of colour (which may be yellowish), odour (which may be faecal, as of bacillus coli), and consistency.



The first two peculiarities are probably owing to the situation in which it occurs, namely in proximity to the intestinal tract, and resulting contamination by *Bacillus coli communis*, or an ally, or its toxins. The third seems to be the effect, for the most part, of long standing. In the cases which are clinically the most acute the fibrin of the sero-fibrinous exudate may be peeled from the peritoneum in sheets and the fluid constituent may be almost entirely lacking.

### *Associated Morbid Conditions.*

In all cases that came to autopsy (88.8 per cent. of this series of 54) peritonitis was not the only morbid condition present. This is probably true also of all the cases that recovered. In the latter 21.2 per cent. there was acute pneumonia on one or both sides, or acute pleurisy, at some time since the commencement of the illness, in 50 per cent. In the other 50 per cent. (or about 10.5 per cent. of all cases) this point remains indefinite. Some came under observation weeks after the onset, and so may well have overcome their lung condition before being seen; in others the chest was not examined. But as in some cases in which no signs in the chest were found during life, on autopsy recent pleural adhesions were found, though there was no active disease, this condition was very probably present in the similar cases that recovered. The view that pneumococcal peritonitis may occur without other lesion does not seem to be correct. The other lesions present in this series were: meningitis; empyaema, single; empyaema, double; empyaema on one side, pleurisy on the other; double pleurisy; pericarditis; endocarditis; arthritis (in one case combined with sub-acute suppurative teno-synovitis); lobar-pneumonia, single; lobar-pneumonia, double; broncho-pneumonia, single; broncho-pneumonia, double; suppurative mediastinitis; acute tonsillitis; otitis media; vaginitis; nephritis; cerebral infarct; tuberculous peritonitis and enteritis (2 cases). Various combinations of these occurred.

### *Diagnosis.*

The clinical diagnosis of pneumococcal peritonitis cannot of course be made with the same accuracy as that of most acute abdominal conditions, as, for example, appendicitis or perforation of viscus, because in that diagnosis, to be scientifically accurate, is involved the identity of bacteria, which cannot be established by clinical means, whereas in the other conditions no such identity is involved. With this proviso, however, and for practical purposes, it can be made quite accurately, but not from the abdominal condition alone, the full history, mode of onset, order of association of symptoms, and examination of the chest being of great importance. This is of course the merest platitude, but seems to be sometimes forgotten in practical life. Difficulty or ease in diagnosis must obviously much depend upon the stage that has been reached in the infection when the case comes under observation.

At the onset, and for the first few hours after this, exact diagnosis is often impossible, because the condition may only be one of some acute infection of probable abdominal origin. In the typical or more usual cases it soon becomes easy, but in the unusual cases (more common, however, in adults than in children) in which at the time of onset there are no signs in the chest and the onset of the abdominal condition is associated with collapse and subnormal temperature, perforation of viscus such as stomach or duodenum may be with difficulty excluded, and if, as sometimes occurs, no accurate history of the health during preceding weeks can be obtained, even perforation of enteric fever may be thought of. The presence of signs in the chest, or a history of pneumonia within two or three weeks, may be suggestive, and absence of previous symptoms of malaise excludes the perforation of enteric fever. If there are no physical signs in the chest the alae nasi may be working, or there may be herpes facialis; there is usually cough with dyspnoea and cyanosis in a pneumococcal case, and the sputum may be rusty and may show the pneumococcus. Signs in the chest develop subsequently in such cases unless death occurs almost at once. As regards the abdomen the absence from the first of localization of pain and deep tenderness to the appendix region, absence of local swelling, the general character of the abdominal rigidity, the general distribution from the first of the superficial tenderness or the first appearance of this in an eccentric site, not McBurney's point, but very early becoming general in any case, the general distribution of the deep tenderness which is not accentuated over the appendix area, and diarrhoea at the onset are suggestive of pneumococcal peritonitis rather than of appendicitis. A marked polymorphonuclear leucocytosis with fibrin network early appears in a pneumococcal case. Leucocytosis will not be present in the case of appendicitis until much later, and then there will be no fibrin network. It is, of course, precisely at the time when exact diagnosis of this condition is of the greatest importance that it is most difficult. For in the conditions with which it is liable to be confused—perforation of viscera of one kind or another—every minute is of importance, and if it is delayed until the picture becomes clear the time for effective action in those conditions will possibly have passed. Therefore laparotomy, which affords the only hope for the other conditions, appears to be the best method of procedure in these doubtful pneumococcal cases.

*When the abdominal effusion has occurred*, there are signs in the chest in nearly all cases. The points of importance are: a history or the presence of pneumonia before the onset of general peritonitis, the mode of onset of the abdominal condition and its particular features, and a leucocytosis of the characters described above.

If seen for the first time in the later stages, when the condition has become subacute, tuberculous peritonitis may be difficult to exclude. In two cases in this series the diagnosis was that of tuberculous disease. To tabulate differences between these two conditions is useless, for the physical signs may be the same. The history, mode of onset, the sputum and its bacteria, the absence

of solid masses on palpation and percussion of the abdomen may be suggestive, but this is all. In some cases of pneumococcal peritonitis, solid masses may be present as in tuberculous peritonitis. This occurred in one case of this series. A leucocytosis of the characters described seems to be conclusive; but the leucocytosis may be indefinite. In two cases of this series both forms of peritonitis were present together, so that diagnosis is sometimes impossible. This condition has more than once been mistaken for ascites, the immediate past history of thoracic disease having escaped notice.

If seen for the first time when the effusion has become localized the diagnosis from appendix abscess and tuberculous peritonitis by the history and mode of onset (provided the chest is examined) can be made upon general principles (history of recent pneumonia within about four weeks from the onset, or physical signs in the chest at the time, mode of onset of symptoms, with special reference to pain, tenderness, and association with vomiting and diarrhoea, character of the leucocytosis, with special reference to the presence of a fibrin network, &c.). But the diagnosis is of course only made certain by bacteriological examination.

Other difficulties are those which occur in the diagnosis between thoracic and abdominal conditions (the well-known cases of pneumonia which present abdominal symptoms at the onset, before lung signs have developed for example). There are two cases in adults known to me in which laparotomy was performed by eminent surgeons, in one upon a diagnosis of acute pancreatitis, in the other upon a diagnosis of acute intestinal obstruction of uncertain origin. In both cases the peritoneal cavity was normal, with the exception, in one case, of a little clear fluid in the abdomen and congestion of the visceral peritoneum over the stomach and upper portion of the small intestine; both subsequently developed frank pneumonia. And such cases as these are commoner in children than in adults. The diagnosis is, therefore, sometimes very difficult, or almost impossible, in this respect. It can, of course, only be made on general principles. Again, cases of peritonitis, general or local, to whatever cause they be due, may develop pneumonia, either as an independent infection or by direct spread of infection from the abdomen. For example, sub-diaphragmatic abscess may infect the pleura and lung (by ulceration). Diagnosis may be difficult when a case comes under observation for the first time in this condition. Whether both conditions or only the lung condition or whether neither condition is due to pneumococcal infection may be difficult to decide. The treatment apart from bacterio-therapy is much the same in any case, but the prognosis is different in each.

### *Prognosis.*

The duration of the condition in cases that recovered was: from the time of onset of abdominal symptoms (pain, vomiting, and diarrhoea) until operation, 25 days (one case), 17 days (one case), 14 days (two cases), 7 days (one

case), uncertain (one case). The total duration of the illness in six cases (from time of first symptom until defervescence) was: shortest over 12 days, longest over 44 days, average about 25 days. Of fatal cases, the duration of illness from time of onset of abdominal condition until death in 14 cases was uncertain, because the onset of peritonitis was insidious. Of the remaining 25, in which the point could be determined, in 12, or less than half, it was under 7 days. In three cases besides the above 12 it was under 14 days; or, in three-fifths of the fatal cases it was under two weeks: 7 days (two cases), 11 days (one case). In ten cases, or two-fifths of fatal cases, it was 14 days or over. Of the total duration of illness from first symptom until death, in six cases (or about one-seventh of fatal cases) it was under one week, the briefest duration being one day. In 14 cases (or about one-third of fatal cases) it was under two weeks. In 16 cases (or about two-fifths of fatal cases) it was under three weeks. In 23 cases (or nearly two-thirds of fatal cases) it was over three weeks. Of four weeks and under there were 20, or about one-half of the fatal cases. Of over four weeks there were 19, or almost as many. Of over six weeks' duration there were 13, or one-third of all fatal cases. The longest case was 90 days, or 12 weeks and 6 days. Two other cases were of 12 weeks' duration.

The prognosis, where all cases are considered together, is bad. Of three cases in adults all died. Of the 54 cases in children in this series only six recovered, giving a total mortality of 88.8 per cent. In the cases where the effusion becomes localized, the prognosis is relatively good, with the qualifications to be presently stated. Of nine cases in this series in which this occurred, six recovered, giving a mortality of 33.3 per cent. for this class. Of the 45 cases in which it did not occur, the mortality was 100 per cent. It is almost unnecessary to say that the cases which recovered were all localized, for this only means that those on the road to curing themselves by localization (and then by absorption or by pointing at the umbilicus or into hollow viscera) were helped out in their cure by surgery. Of the three cases that became localized but died, in one there was no autopsy, the other two showed old general adhesions. In one other case the collection had become localized; but death resulted from perforation of intestine during operation, so it is excluded from this set. There were old generalized adhesions throughout the peritoneum. In all cases, whether the effusion is generalized, or, at the time of operation, localized, the outlook depends not so much upon the peritoneal condition, which is relatively amenable to surgical treatment, as upon the fact that in any case there may be present, or develop subsequently, acute pleurisy or pneumonia (single or double), pericarditis, endocarditis, meningitis, arthritis, &c., but chiefly that there is septicaemia which has been present from the first. Any of these conditions may be fatal after the peritonitis has been adequately dealt with surgically. The above conditions are, of course, less likely to occur in cases where localization occurs, because such cases represent milder infections or greater powers of resistance than the others. Yet they may occur and prove

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### *Prognosis.*

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peritonitis is made. Earlier diagnosis would help in a similar way. But it seems clear that surgical treatment is here only of secondary importance, though essential to assist other measures in most cases.

It is obvious that in the matter of serum therapy nearly everything depends upon the native powers of the patient. Nothing is done by such measures to eliminate the organism from the circulation, to control its action, to minimize the dose or to lower its virulence. The only hopeful treatment as a whole for pneumococcal peritonitis, as for the other conditions arising in pneumococcal infections, is by bacterio-therapeutic methods, by an antipneumococcal serum or vaccine which shall deal with their cause—septicaemia. Considering the large number of different strains of pneumococci present in these cases, it would seem to be necessary to manufacture a vaccine for each case. Since, however, the more severe cases are so very acute, and the time-element therefore is of great importance, it seems open to question how far this treatment will be practicable. In the more usual cases, however, which become subacute or almost chronic and last for weeks, the time-element is not of such importance, and in them this difficulty would not appear to arise. In view of the teachings of experience of other conditions such as empyema, however, drainage of collections of inflammatory fluid as a routine measure would appear to be almost always essential to assist this method to success. No administration of Pane's or Römer's antipneumococcic sera or Sir A. Wright's vaccine was undertaken in any of these cases.

## REFERENCES.

1. Banti, *Lo Sperimentale*, Firenze, 1889, lxiii, 138.
2. Carmichael, *Med. Press and Circular*, London, 1907, N.S. lxxx, iii, 278.
3. Dieulafoy, *Presse méd.*, Paris, 1899, xc, 281.
4. Eyre, *Journ. Path. Bact.*, Edinb., 1906, xi, 246.
5. Flexner, *Johns Hopkins Hosp. Bull.*, Baltimore, 1895, vi, 64.
6. Fowler, *Scottish Med. and Surg. Journ.*, Edinb., 1903, xii, 177.
7. Fraenkel, *Deutsche med. Woch.*, Leipzig, 1901, xxvii, 28.
8. Gaillard, *Bull. et Mém. Soc. méd. hôp. Paris*, 1890, 3<sup>e</sup> sér., vii, 871.
9. Jensen, *Langenbeck's Archiv für klin. Chirurg.*, Berlin, 1903, lxi, 1134.
10. Lennander, *Deutsche Zeitschr. f. Chir.*, 1902, lxiii, 1.
11. Marchisio, *Gazz. d. osp. Milano*, 1906, xxvii, 181.
12. Ménétrier et Legroux, *Bull. et Mém. Soc. méd. hôp. Paris*, 1900, 3<sup>e</sup> sér., xvii, 882.
13. Picker, *Centralbl. für d. Krankh. d. Harn- und geschl. Org.*, Leipzig, 1905, xvi, 123.
14. Prochaska, *Deutsches Arch. für klin. Med.*, 1901, lxx, 559; *Centralblatt für innere Med.*, Leipzig, 1900, lxvi, 1145.
15. Rosenow, *Journal Inf. Dis.*, Chicago, 1904, i, 280.
16. Schultz, *Int. Arch. d. Sci. biol. de St.-Petersb.*, 1901, viii, 1.
17. Selter, *Zeitsch. für Hygiene und Infektionsk.*, Leipzig, 1906, liv, 363.
18. Sevestre, *Bull. et Mém. Soc. méd. hôp. Paris*, 1890, 3<sup>e</sup> sér., vii, 467.
19. Walther, *Semaine méd.*, Paris, 1897, xvii, 199.
20. Washbourn, *Lancet*, Lond., 1902, ii, 1301.
21. Weichselbaum, *Wiener klin. Wochenschr.*, 1888, xxviii, 573; *Centralbl. f. Bact. u. Paras.*, Jena, 1889, v, 1.
22. Wolf, *Journal Inf. Dis.*, Chicago, 1906, iii, 446.

# A RÉSUMÉ OF SOME OF THE EVIDENCE CONCERNING THE DIAGNOSTIC AND CLINICAL VALUE OF THE WASSERMANN REACTION

By HUGH WANSEY BAYLY

## *Introductory.*

THE evidence that has accumulated during the last four years seems to speak with no uncertain voice as to the value of the serum diagnosis of syphilis. The test has been given very extensive trials by conscientious workers all over the world, and the literature on the subject has become so large as to render it difficult for most busy physicians, surgeons, or gynecologists to arrive at the data on which a favourable opinion as to the great value of this test has been based. As the original technique as described by Wassermann was somewhat complicated, requiring the use of laboratory animals and sheep's blood, it has necessarily followed that numerous workers have endeavoured to simplify the technique so as to bring it within the reach of others than the clinical pathologist. It is remarkable that though innumerable modifications and simplifications have been introduced during the last two years the consensus of expert opinion is still strongly in favour of the original technique, or of such slight modifications of the original method as do not necessitate the substitution of variant factors for constant factors.

At the discussion on complement fixation that was opened by Wassermann before the combined Pathological and Bacteriological Sections of the British Medical Association in July last, practically all the speakers were in favour of the original technique as compared with the simplified techniques advocated by Hecht, Brauer, Fleming, Stern, &c. In this short review I do not propose to discuss any questions of technique, and shall only deal with some of the evidence that has accumulated as to the value of the test as a means of diagnosis and as a control of treatment. I consider, however, that for the best results to be obtained the original or an only slightly modified technique should be employed, and that the test should be carried out by a laboratory worker experienced in the use of such technique.

The first question to be settled is whether the reaction is sufficiently specific to render the test a reliable one for the diagnosis of syphilitic infection. Wassermann states that out of 10,000 sera examined, he has not once diagnosed syphilis wrongly, and Hochne only obtained two positive results out of 1,100

sera taken from healthy persons or patients suffering from diseases other than syphilis, and in neither of these two could syphilis be excluded. McDonagh, Müller, and Morawitz, in reporting 5,000 cases examined by them in Finger's clinic, state that they did not obtain a single positive result in any case where syphilis could be definitely excluded; and Blaschko, of Berlin, as the result of the examination of 900 cases, found the result in accordance with the clinical diagnosis in all but 30 cases. Out of 50 sera examined by Beckers, and taken from patients with tuberculosis, typhoid, scarlet fever, arterio-sclerosis, and heart failure, only two gave a positive reaction, in neither of which syphilis could be excluded. Jenonck and Meirowski examined 110 certainly non-syphilitic cases, and only found one positive result, which was that of a child dying with tuberculous meningitis, and they and other observers have recorded that a positive result is often obtained with dying persons or cadavers.

Statistics taken from very many thousands of observations made by observers in England, France, Germany, Austria, Sweden, America, and Australia, show that of all cases of syphilis examined, from 80 to 90 per cent. give a positive reaction. The percentage differs but slightly with different observers. I myself have determined the reaction in over 500 untreated or but slightly treated cases, and obtained a positive reaction in 85 per cent.

The percentage of positive reactions obtained varies considerably with the period of the disease and whether the disease is acute or latent. Thus primary cases in which the lesion has been present for less than a fortnight almost invariably give a negative reaction, while 75 per cent. of positive reactions are obtained if the primary sore has been present for over a month. Secondary syphilis with symptoms gives a positive result in over 90 per cent. of cases and tertiary syphilis in about 75 per cent. In cases of latent syphilis (viz. syphilis without symptoms) the early cases give a positive reaction in 75 per cent. and the late cases in 76 per cent. in the untreated cases. (See Table I.) The results obtained with the parasymphilitic diseases, tabes and general paralysis, are given in Table VI. Different results are obtained with different tissues; thus a very high percentage of positive results is obtained with aneurysm of the aorta, and only a low percentage with cerebral syphilis.

### *Effect of Treatment.*

The effect of mercurial treatment is usually clearly seen, and depends on the time in the history of the infection that treatment began, and the length and nature of the treatment. (See Tables II and III.) Potassium iodide and the early arylarsonates (atoxyl, soamin, and orsudan) seem to have but little, if any, action on the reaction. Neisser has observed that the earlier in the course of the disease that treatment is commenced the more probability there is that a negative result will be obtained after a course of treatment. Where treatment began as soon as possible after the primary lesion had appeared, 75 per cent. of negative reactions were subsequently obtained, whereas, if treatment had been



delayed for six months, only 33 per cent. of negatives were obtained after treatment.

Of late latent cases (that is, cases several years after infection in which there are no symptoms) he found that the early treated cases gave negative results in 80 per cent. of cases, and the late treated cases in only 58 per cent. Pürckhauer reports the result of treatment on 165 cases at different stages of the infection, all of which were positive before treatment. Of 116 primary and secondary cases 75 per cent. became negative immediately after treatment. Of 12 early latent cases 4 became negative, of 15 late latent cases 4 became negative, and of 18 tertiary cases only 2 became negative. Of 4 cerebral cases only one became negative after treatment. The longer infection has persisted the more stable the positive reaction seems to become, and the greater difficulty there is in inducing a negative reaction by treatment; and in some late tertiary and parasyphilitic conditions a negative reaction is never produced even by the most rigorous mercurial treatment.

Occasionally a case is diagnosed as syphilis and gives a negative reaction, and yet after being on mercury for a while a positive reaction is obtained. This is probably due to the fact that the mercury destroys numbers of the treponemata, whose endotoxins are then liberated, and stimulate the production of the antibody which is probably the substance which produces the positive reaction. If 5 per cent. of complement is fixed the case must be reported as positive, and 10 per cent. of complement is only used in order to obtain a rough idea of progress under treatment. Active syphilis will generally deviate 10 or 15 per cent. of complement, but as the infection becomes less the amount of complement deviated also becomes less. In this way it is possible to make a rough quantitative measurement of the amount of complement fixed and of the progress made under treatment, even though the case must still be returned as 'positive'. Using this method I have compared the therapeutic value of some of the different methods of administering mercury. Pills and suppositories seem to be the slowest and least efficient forms of treatment, and inunctions and intramuscular injections of insoluble compounds the quickest and most efficient. (See Tables II and III.) Harrison's instructive series shows clearly the *influence* of only short treatment, for, although the percentage of 'positives' remains high, some effect of treatment is recorded in 69 per cent. of cases after only one course. With pills, on the other hand, 97 per cent. of cases treated for six months or under are positive, and only 8.5 per cent. show any effect of treatment. When the inunction method was employed, after three months' treatment only 16.6 per cent. remained positive. Daily inunction is obviously an inconvenient method of treatment, and all skins do not tolerate this method, but otherwise inunction would seem by this too short series to be the most satisfactory form of administration of mercury. Intramuscular injection, however, appears almost though not quite as potent, and to be undeniably superior to pill treatment. That it is not the presence of the mercury itself in the blood that produces a negative reaction, was shown by Brauer, who

demonstrated that a strong positive can be obtained when the mercury excretion in the urine is most marked, and that a negative reaction may be present when the mercury excreted in the urine is weak or absent. He showed that a previous negative reaction may become positive in spite of a large quantity of mercury in the blood, and that a reaction which has become negative under treatment can become positive in spite of mercury persisting in the urine.

With the Ehrlich-Hata '606' preparation (dioxy-diamydo-arseno-benzol) very varying results as regards the Wassermann reaction are recorded in the literature. (See Table IV.) Emery of Paris writes: 'Regarding the reaction of Wassermann, which will allow us to determine and appreciate by its course the regression of infection, it becomes negative at intervals varying from three weeks to two months. The disappearance takes place slowly and progressively without undergoing the oscillations which are met with in mercurial cures.' Zeiler reports several cases which became negative at various periods after injection with '606' but which later returned to positive. The history of the use of this new remedy is too recent to enable us to know whether the negative reaction which is obtained in the majority of cases is permanent. The earlier reports, in which negative reactions were almost invariably recorded as present in a week to a fortnight after injection, seem to have been too optimistic, and of the only six cases that I have personally examined one was negative three weeks, four were positive three weeks, and one was positive six weeks after injection.<sup>1</sup>

Nearly all authorities, both Continental and American, including Ernest Lane and Charles Gibbs of this country, agree that in future treatment, whether by mercury or '606', must be regulated by the Wassermann reaction. A solitary negative reaction obtained with the serum of a patient undergoing mercurial or '606' treatment means little but that the patient is reacting to the treatment. A series of negative results taken at intervals of three to six months after all treatment has been given up is necessary before the patient can be regarded as cured, and even then until another twenty years have passed we cannot be absolutely certain that the disease is completely and permanently obliterated, and that no late manifestations will ever occur. It is important to remember that about 10 per cent. of untreated cases of syphilis fail to give a positive reaction at the first examination, and that therefore a negative reaction only gives a 90 per cent. *probability* of freedom from infection. If, in *recently acquired syphilis*, after several months' treatment the reaction still remains strongly positive and large doses of complement are still fixed, it is an indication that the treatment is inefficient, and that more rigorous methods should be adopted. If, however, after each course of treatment a smaller amount of complement is fixed, or the intervals before a positive reaction returns become longer and longer, we may conclude that the treatment is satisfactory, and that there is no necessity to increase the dose.

<sup>1</sup> Of these cases all but one, however, became negative one month later.

If we judge the efficacy of treatment by the period of time elapsing between the commencement of the treatment and the onset of the effect of treatment, as shown by the Wassermann reaction, it would appear that '606', mercurial inunctions, intramuscular injections of insoluble mercurial compounds, suppositories, and oral treatment must be arranged in the order named. A few cases remain positive after three or more years' treatment, and it is therefore obvious that no fixed time for treatment can be laid down. Three years, however, seems to be the shortest period for mercurial treatment that can be advised with any safety, and this of course must be prolonged if the Wassermann reaction is, or becomes, positive.

### *Specificity of Reaction.*

Of the diseases certainly not syphilitic in which a positive reaction is obtained, Yaws heads the list, and in this disease as high a proportion of positives is obtained as with syphilis itself: Baermann obtained 90 per cent. of positives in untreated cases. Leprosy also produces a high percentage of positive results, Baermann reporting 40 per cent. and Noguchi 80 per cent. Meier also reported that the majority of cases give a strongly positive result. It appears, however, only to be the tuberculous form of the disease that produces a positive reaction. Trypanosomiasis has been reported frequently to give a positive reaction, but I have been unable to obtain any statistics for the reaction in this disease. In malaria, Baermann obtained 20 per cent. positive in untreated cases with fever and 4 per cent. positive in treated cases without fever. Of fifty sera (tuberculosis, typhoid, scarlet fever, arteriosclerosis, and heart failure) examined by Beckers, only two gave a positive reaction, and in neither of these cases could syphilis be excluded. Scarlet fever was at first believed frequently to produce a positive reaction, and Much reported fifty-nine positives out of 130 cases examined.

Later observers have, however, failed to confirm his figures, and have only obtained positive results very rarely. In any case the positive reaction is said to be very transient, and Blaschko has observed that when the positive result does occur it is not till about fourteen days after the rash that it appears, and that it disappears within three months. Weil and Braun and myself have reported thirty-six cases of pneumonia in which a positive reaction was obtained in eleven. I found that the positive reaction did not appear till after the crisis and only lasted a few days. Weil and Braun have also reported three positive results out of twenty sera taken from typhoid patients. No case of heart disease in which syphilis can be excluded has been reported as giving a positive reaction. Very many cases of aneurysm of the aorta give a positive reaction, but in the majority a history of syphilis can be obtained. Bassett-Smith has informed me that under his report of late secondary and tertiary syphilis giving positive reactions, he included many cases of aneurysm, chronic endo-

carditis, and cases with cerebral symptoms in which a distinct history of syphilis had been obtained. One case of beri-beri gave a negative reaction.

Cancer or tuberculous infection practically never gives a positive reaction in cases in which syphilis can be excluded. The reports of various observers as regards the reaction in various diseases will be found in Table V. Reinhart has not obtained a single positive result in malignant disease, phthisis, typhoid, pneumonia, nephritis, leukaemia, pernicious anaemia, diabetes, measles, or diphtheria, but he has recorded positive reactions in scarlet fever and malaria. I have not succeeded in finding any extensive records of the reaction in various nervous diseases, but I shall hope to be in possession of the necessary data in a few months. Table VI gives the results obtained by different observers in parasyphilis. Out of 432 cases of general paralysis reported by various observers and collected by Noguchi, 90 per cent. gave a positive reaction with cerebrospinal fluid, while of fifty-two cases of tabes only 56 per cent. were positive. Of thirty-four cases of cerebrospinal syphilis only 19 per cent. were positive with cerebrospinal fluid, and only about the same percentage was obtained with serum.

If the cerebrospinal fluid of persons suffering from secondary or tertiary syphilis, in which there is no special involvement of the central nervous system, be examined a negative reaction is usually found, but in parasyphilitic conditions where the central nervous system is primarily involved a higher percentage of positive results may be obtained with the cerebrospinal fluid than with the serum. This is particularly noticeable with general paralysis. Mott has suggested that it is a question of cell destruction, and that the greater cell destruction that occurs in general paralysis is the cause of the higher proportion of positive results as compared with tabes. It would be interesting to note if cases of tabes giving a positive reaction showed more improvement under mercurial treatment than those cases where the reaction was absent. In 100 cases of disease of the nervous system of a non-syphilitic nature examined by Reinhart, not a single positive reaction was recorded. The cases included true epilepsy, multiple sclerosis, myelitis, neuritis, alcoholic pseudo-tabes, and cerebral tumour.

Bayet considers that as regards the question of marriage and offspring, the serum diagnosis, contagiousness, and the transmission of infection to offspring must be regarded as three distinct matters. He thinks that clinical experience must be considered of equal value with the Wassermann reaction, and the questions of age of infection, length and nature of treatment, and time since the last appearance of any symptoms must be thoroughly gone into when the practitioner is asked his advice as to the permissibility of marriage. He does not consider a positive Wassermann reaction an *absolute* contra-indication to marriage, providing that *all* other considerations are satisfactory. If, however, marriage of a man giving a positive reaction is permitted and pregnancy occurs, he advises that the mother should undergo antisyphilitic treatment even if she presents no symptoms and gives a negative Wassermann reaction.

If we judge the efficacy of treatment by the period of time elapsing between the commencement of the treatment and the onset of the effect of treatment, as shown by the Wassermann reaction, it would appear that '606', mercurial inunctions, intramuscular injections of insoluble mercurial compounds, suppositories, and oral treatment must be arranged in the order named. A few cases remain positive after three or more years' treatment, and it is therefore obvious that no fixed time for treatment can be laid down. Three years, however, seems to be the shortest period for mercurial treatment that can be advised with any safety, and this of course must be prolonged if the Wassermann reaction is, or becomes, positive.

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TABLE II. *Effect of Treatment with Intermuscular Injections.*

	No. of Cases.	+ with 0.2 Comp.	Additional + with 0.1 Comp.	% showing some effect of treatment.	Total. +	% +
After 1 course (of 3 months)						
Harrison . . . . .	55	17	29	69	46	83.6
Bayly . . . . .	32	21	7	34.4	28	87.5
After 2 courses						
Harrison . . . . .	49	24	14	51	38	77.5
Bayly . . . . .	16	7	6	56.2	13	81.2
After 3 courses						
Harrison . . . . .	42	8	19	80.9	27	64.5
Bayly . . . . .	4	1	1	75	2	50
After 4 courses						
Harrison . . . . .	30	3	14	90	17	56.5
After 5 courses						
Harrison . . . . .	34	4	13	88.2	17	50
After 6 courses						
Harrison . . . . .	26	3	6	88.4	9	34.6

TABLE III. *Effect of Treatment on Wassermann Reaction.*

Nature of treatment.	Length of treatment.	No. of Cases.	Positive with 0.1 Comp.	% +	Positive with 0.2 Comp.	Partial or complete Haemolysis with 0.2.	% showing some effect of treatment.
Pills	6 months	35	34	97.1	32	3	8.5
	or under	(66)	(62)	93.9			
	6 months	15	11	73.3	5	10	66.6
	to 1 year	(33)	(19)	57.5			
	1-1½ years	13	9	69.2	1	12	92.3
		(25)	(10)	40.0			
	1½-2 years	12	5	41.6	1	11	91.6
Inunctions	Under 3 months	10	10	100	8	2	20
	3 months	6	1	16.6	1	5	83.3
	6 months	4	0	0.0	0	4	100

The cases in brackets were only tested with 0.1 of complement.

TABLE IV. *Effect of Treatment with '606'.*

Observer.	Number of Cases.	% negative after treatment.
Glück . . . . .	20	100
Harrison (L. W.) . . . . .	71	{ 50 after 4 weeks 88 after 5 weeks
Lange . . . . .	268	63
Miekeley . . . . .	65	14
Neisser (A.) . . . . .	?	44 (doubts permanency)
Nicolich and Favento . . . . .	?	66
Saalfeld . . . . .	26	0
Schreiber and Hoppe . . . . .	52	84 { earliest 4 days latest 70 days
Wechselmann . . . . .	?	Nearly 100

TABLE V. *Reaction in Various Diseases.*

	<i>Typhoid.</i>		<i>Scarlet Fever.</i>		<i>Tuberculosis.</i>		<i>Carcinoma.</i>		<i>Morbus Cordis.</i>	
	Cases.	Pos.	Cases.	Pos.	Cases.	Pos.	Cases.	Pos.	Cases.	Pos.
Bassett-Smith . . . . .	3	0	7	1	9	0			11	0
Bayly . . . . .	6	0	20	1	22	0	34	0	10	1 <sup>1</sup>
Jochmann . . . . .			33	0						
Meier . . . . .			52	0						
Much . . . . .			130	59						
Noguchi . . . . .			63	3 <sup>2</sup>	52	0	51	3 <sup>2</sup>		
Weil and Braun . . . . .	20	3								
Gastau . . . . .										
Donath . . . . .										

<sup>1</sup> History of old syphilis obtained.<sup>2</sup> Two of these were doubtful results.

TABLE V (continued).

	<i>Pneumonia.</i>		<i>Gonorrhoea.</i>		<i>Acute Rheumatism.</i>		<i>Various Skin Diseases.</i>		<i>Nephritis.</i>		<i>Disease of Aorta.</i>	
	Cases.	Pos.	Cases.	Pos.	Cases.	Pos.	Cases.	Pos.	Cases.	Pos.	Cases.	Pos.
Bassett-Smith . . . . .			39	0	4	0	39	0	2	0	Many cases positive	
Bayly . . . . .	24	7	25	1 <sup>3</sup>	3	0	5 <sup>4</sup>	5	5	0		
Noguchi . . . . .							58	1			6	5
Weil and Braun . . . . .	12	4									24	16
Gastau . . . . .											27	33
Donath . . . . .												

<sup>3</sup> Syphilis could not be excluded.<sup>4</sup> Leucoderma cervicis.

TABLE VI.

*Tabs.**General Paralysis.*

	<i>Serum.</i>			<i>Cerebrospinal Fluid.</i>			<i>Serum.</i>			<i>Cerebrospinal Fluid.</i>		
	No.	Cases.	% +	No.	Cases.	% +	No.	Cases.	% +	No.	Cases.	% +
Noguchi . . . . .	205		60	11		54	61		65	60		73
Marie and Levaditi . . . . .				9		66						
Wassermann . . . . .				15		53				35		94
Mott, Chandler, and Henderson } Smith										64		92
Bayly . . . . .	10		50				10		80			

TABLE VII. *Nervous Diseases.*

	<i>Bassett-Smith.</i>	<i>Noguchi.</i>	<i>Bayly.</i>
Neurasthenia . . . . .	28-0		
Hemiplegia . . . . .	9-0	8-3	3-1
Insanity . . . . .	6-0	24-4	
Epilepsy . . . . .	3-0	69-12	6-0
Tumour of brain . . . . .		8-4	4-2
Spastic paraplegia . . . . .		3-2	
Dementia praecox . . . . .		131-15	

TABLE VIII *Reaction in Eye Cases.*

	<i>Interstitial Keratitis.</i>		<i>Iritis.</i>		<i>Choroiditis.</i>	
	Cases.	% Pos.	Cases.	% Pos.	Cases.	% Pos.
Leber . . . . .	?	84	?	33	?	28
Harman . . . . .	12	100	4	25	5	100 <sup>1</sup>
Noguchi . . . . .	12	66	6	66		
Bayly . . . . .	7	100				

<sup>1</sup> These cases were diagnosed as 'probably syphilitic' before examination of serum.

## REFERENCES

1. Baermann, G., *Münch. med. Woch.*, 1910, lvii. 2131-2135.
2. Bar and Daunay, *L'Obstétrique*, 1909, 177 and 260.
3. Bassett-Smith, *Brit. Med. Journ.*, 1910, ii. 1434.
4. Bayet and Renaux, *Le sérodiagnostic de la syphilis*.
5. Bayly, H. W., *Lancet*, 1909, i. 1523.
6. Bayly, H. W., *West Lond. Med. Journ.*, 1910.
7. Bayly, H. W., *The Med. Mag.*, 1910, 326-332.
8. Bayly, H. W., *Proc. Roy. Soc. Med.*, Lond., 1909-10, iii. 3; Surg. Sec. 238.
9. Bayly, H. W., *Brit. Med. Journ.*, 1910, ii. 1430.
10. Beckers, J. K., *Münch. med. Woch.*, 1909, lvi. 551-552.
11. Brauer, A., *ibid.*, 1910, lvii. 505-507.
12. Bruck and Stern, *Deutsch. med. Woch.*, 1908, xxxiv. 401.
13. Donath, *Münch. med. Woch.*, 1909, lvi. 946; *Berl. klin. Woch.*, 1909, xlvii. 2015-2018.
14. Destre, L., *Wien. klin. Woch.*, 1908.
15. Ehrlich, Prof., *Deutsch. med. Woch.*, 1910, xxxvi. 1893.
16. Emery, E., *Lancet*, 1910, ii. 1543-1548.
17. Gastau and Giraud, *Diagnostic de la Syphilis*, 1910.
18. Gibbard, T. W., and Harrison, L. W., *Journ. Roy. Army Med. Corps*, Lond., 1910, xv. 587.
19. Gibbs and Bayly, *Lancet*, 1910, i. 1256.
20. Glück, A., *Münch. med. Woch.*, 1910, lvii. 1638-1641.
21. Harman and Brunt, *West Lond. Med. Journ.*, 1910.
22. Harrison, L. W., *Journ. Roy. Army Med. Corps*, Lond., 1910, xv. 52.
23. Hochne, F., *Med. Klin.*, 1908, v. 1787-1790.
24. Jochmann, *Münch. med. Woch.*, 1908, lv. ii. 1690.
25. Lane, J. E., *Proc. Roy. Soc. Med.*, 1909-10, iii. 3, 209-219; Surg. Sec.
26. Lange, C., *Berl. klin. Woch.*, 1910, xlvii. 1656-1659.
27. McDonagh, Müller, and Morawitz, *Practitioner*, 1909, lxxxiii. 307-327.
28. Marinesco, *Comptes Rendus Soc. de Biologie*, 1909, lxvi. 648.
29. Meier, G., *Med. Klin.*, 1908, iv. 1383.
30. Miekley, *Deutsch. med. Woch.*, 1910, xxxvi. 1903.
31. Mott, *Brit. Med. Journ.*, 1909, i. 1403.
32. Neisser, *Berlin. klin. Woch.*, 1910, xlvii. 1485-1490.
33. Neisser, *Deutsch. med. Woch.*, 1910, xxxvi. 1889.
34. Nicolich and Favento, *Münch. med. Woch.*, 1910, lvii. 2080-2082.
35. Noguchi, H., *Serum diagnosis of Syphilis*, 1910.
36. Pürckhauer, R., *Münch. med. Woch.*, 1909, lvi. 698-702.
37. Reinhart, A., *Münch. med. Woch.*, 1909, lvi. 2092-2097.
38. Schreiber, *Deutsch. med. Woch.*, 1910, xxxvi. 1898.
39. Stern, Carl, *ibid.*, 1910, xxxvi. 1908.
40. Wassermann, A., *Brit. Med. Journ.*, 1910, ii. 1427.
41. Wechselmann, *Deutsch. med. Woch.*, 1910, xxxvi. 1901.
42. Weil and Braun, abstr. in *Münch. med. Woch.*, 1908, lv. 1450.
43. Zeiler, K., *Deutsch. med. Woch.*, 1910, xxxvi. 2040-2044.



## CRITICAL REVIEW

### VERTIGO<sup>1</sup>

By SYDNEY SCOTT

#### *Nomenclature.*

THE terms dizziness, giddiness, and vertigo are frequently used in a synonymous sense. Etymologically *dizziness* is, according to Skeat, derived from the Anglo-Saxon *dysig*, Danish *dösig*, Old High German *túsic*, and meant *dull, stupid*, hence *confused*. *Giddiness* has a different derivation and comes from the Anglo-Saxon *gyð*, a song: *gyddian* to sing, hence probably dancing, whirling, wild, unsteady. *Vertigo* has a more concise origin from the Latin *verto*, I turn, I reel. These terms are to be regarded as representing in this article the French *le vertige*, and the German *schwindel*.

#### *Introductory.*

Vertigo is one of the clinical manifestations produced by disturbances in the system of co-ordination. To comprehend its significance it is necessary to understand in at least a general way that branch of the nervous system which is concerned with the functions of equilibration. As it is proposed to discuss chiefly the clinical significance of vertigo, we must content ourselves with recalling some points which are known to have a physiological bearing on the subject, and shall assume a general knowledge of the anatomy of structures to which we refer (3, 34, 41, 42, 50, 76, 101, 113, 148). It may be taken for granted that in normal states of consciousness we possess a correct perception of position, a true topographical knowledge of ourselves as a whole, and of our surroundings in relation to space. These perceptions are derived from nerve impressions received from different parts of the body:

Group I. Without particularizing too laboriously we may regard the

<sup>1</sup> This paper represents hardly more than an introduction to the subject of vertigo: certain features only are emphasized: much that is familiar has been omitted: only references which have been consulted have been given: in certain instances the author has availed himself of reviews and has endeavoured to acknowledge the reviewer, although in some cases the name was not always noted. Such omissions in the bibliography were undesigned. The bibliography is obviously incomplete when we have regard to the literature available.

impressions upon which we directly depend for perceptions of our own position (subjective orientation) as being derived from the following sources:—  
 1. Vestibular or labyrinthine. 2. Muscular. 3. Tendinous. 4. Ligamentous. 5. Articular. 6. Visceral (pressure due to gravity and muscular action).

Group II. The impressions which give rise to perceptions of the position of our surroundings (objective orientation) are:—1. Visual. 2. Auditory.

Group III. In this group we include impressions (excluding 'referred' sensations) which enable us to perceive concurrently the position both of ourselves and of the external agent which provokes the impression in relation to one another. Cutaneous: (a) Tactile. (b) Pressure. (c) Thermal. (d) Painful.

A moment's consideration of the above impressions, as arranged in these three groups, will readily bring to mind many instances in which a knowledge of change of position of our surroundings influences the perception of our own position in space. Objective orientation affects subjective orientation, and *vice versa*, or in Bonnier's words, 'l'orientation objective est conditionnée par l'orientation subjective' (20).

Both perceptions are, moreover, closely dependent upon and intimately related to muscular accommodation, particularly in the maintenance of the erect position of the body and in locomotion. The importance of the correlation between these impressions by means of a system of co-ordination with motor centres is self-evident. The extent and intensity of reflex muscular action (which includes muscular relaxation as well as muscular contraction (139)) are directly influenced by the degree and extent of the corresponding afferent impressions which give rise to out-going muscular impulses.

The impressions which have been mentioned do not all enter consciousness as sensations, and yet they produce what we may term an *impression-complex* on the centres of co-ordination situated for the most part in the cerebellum and corresponding regions of the cerebrum.

Contraction and relaxation (139) of various muscle-groups are controlled by the particular impression-complex which at any given moment holds sway. When the components of this complex are in perfect accord the effect is correct orientation and maintenance of equilibrium: vertigo results from discord between these components.

From the writings of Hughlings Jackson we learn that vertigo should be regarded as 'the state of consciousness of the effect of this want of harmony between afferent impressions on motor centres'. The mere consciousness of discord between in-coming impressions does not constitute vertigo (58). Vertigo is then not a malady in itself, nor is it the only manifestation of inco-ordination. It is a particular state of consciousness, induced by different physiological and pathological causes, which play their part through interfering with one or other of the above-mentioned impressions.

In clinical as in experimental vertigo we shall show that the vestibular, retinal, or muscular-sense impressions are the ones most frequently disturbed.

According to Gowers (58), labyrinthine vertigo is by far the commonest variety of vertigo met with.

*Various Types of Subjective Sensations in Vertigo.*

The sensations of vertigo in consciousness vary in kind and degree. In the most typical form the individual feels as though he were suddenly turned round and round about a longitudinal axis, or that he were impelled forwards or backwards around a transverse horizontal axis or to one side or other around an antero-posterior horizontal axis.

He may also imagine that objects are revolving around him in corresponding planes. Such sensations may be accompanied by a reeling or tottering gait, or they may be so sudden and intense that the balance for the moment is completely lost. Vertigo may be accompanied by nausea, vomiting, headache and a feeling of faintness, and muscular weakness. The face becomes pallid, and the skin covered with clammy sweat, the pulse feeble. Mental processes are confused, while memory for the distressing sensations is retained. Rarely is vertigo associated with loss of consciousness (129, 151). In other forms of vertigo faintness, nausea, and vomiting are absent, and fair muscular control may be retained. Even a tendency to reel may be inhibited. Vertigo generally occurs during waking hours, but nocturnal attacks which awaken the patient are not uncommon.

The sensation in the milder forms, or at the commencement of attacks which increase in severity, consists of a consciousness of uncertainty of position of self; of 'a swimming feeling in the head', or 'a mistiness before the eyes' (46). There may be a sensation of change in subjective or of objective position in an uncertain direction. As the feeling of apparent movement becomes more intense the idea of direction becomes more definite; in many cases the consciousness is so confused by conflicting impressions, that no clear perception of the apparent principal direction of movement is gained.

Some patients describe their sensations as similar to that of falling from a height or of 'sinking'. It seems curious that such sensations should be the same whether the patient is standing, lying, or whatever the position of the head, but we do meet with these descriptions even in patients who have definite signs of labyrinthine disease. It is rare for patients to have the reverse sensations, namely that of rising or 'walking on air'. The transepithallic galvanic current may occasionally produce such a feeling.

Sometimes the attention of the patient is concentrated upon an apparent movement of external objects. 'The room seems to be going round', or 'the ground seems to rise', or 'everything seems to lean to one side'.

We see patients who tell us they 'feel as if falling backwards, while the ground seems to suddenly rise upwards and hit them in the face', whereas they must have suddenly been hurled forwards on to the ground.

In considering the sensations of patients during vertigo we have to inquire

into the (1) sensations of apparent change of position of self (disturbed subjective orientation); (2) sensations of apparent change of position of surroundings (objective orientation); (3) sensations of the forced movements, and the character of motor inco-ordination. For an account of the sensations in vertigo we are dependent upon the descriptions given by the individual himself, whereas the type and character of forced movements are signs which must be independently observed. These movements include deviation of the eyeballs and of the head, nystagmus and ataxic gait; certain other modified purposeful movements.

Grainger Stewart and Gordon Holmes in their classical monograph on the Symptomatology of Cerebellar Tumours (145) paid particular attention to the sensations of vertigo in these diseases, with respect to subjective and objective orientation. These observers were able to distinguish the types of vertigo in intracerebellar from those met with in extra-cerebellar lesions. We should have expected extra-cerebellar lesions to give rise to the same kind of sensations as those produced by labyrinthine lesions, and in many respects this is true. Stewart and Holmes, however, noted that in their 22 cases the sense of rotation of self was 'towards the lesion in extra-cerebellar' tumours and 'away from the lesion in intracerebellar' tumours. Oppenheim (114), however, thinks the sensations of patients are too unreliable to make so definite a distinction; and as regards pure labyrinthine lesions it is certainly true that patients do not agree as to the sense of direction of movement both as regards subjective and objective orientation; and, moreover, pure unilateral labyrinthine lesions will occasionally give rise to the same order of sensations as those described by the Queen Square Hospital patients who had intracerebellar tumours. It is possible to account for this difference in the sensations of apparent movement when we take into consideration the researches of F. S. Lee (93) in the labyrinths of elasmobranchs. This observer found that a 'slight pressure' applied to an ampullary nerve caused deviation of the eyes in one direction, while 'greater pressure' caused deviation of the eyeballs in the opposite direction. This, together with other considerations, led to the hypothesis of 'principal' and 'subordinate' functions for each ampullary division of the vestibular nerve, an hypothesis in favour of which further evidence has been obtained by observations in the human subject (135). Each ampullary nerve will then convey stimuli which produce reflex *movements and sensations of movements in a certain plane, and the direction of these movements depends upon the character of the stimulus*; 'kathodal galvanic current' producing movement and sensation of movement in one direction and the 'anodal currents' the same movements in the opposite direction. By varying the temperature of 'caloric stimuli', and by altering the degree of pressure in 'pressure stimuli', a reversal of direction of reflex movement and of the sensations of movement can be produced (11, 22, 38, 45, 92, 93, 98, 135).

What applies to labyrinthine stimulation and lesions may well apply to extra-cerebellar lesions, and the perception of direction in the sensations of giddiness depends probably not on intellect, but upon the exact source and intensity of the stimulus.

For these and other reasons we think with Oppenheim (114) that the direction in consciousness of apparent movement is not reliable in seeking to establish a diagnosis of localization, certainly as regards peripheral lesions.

### *Forced Movements.*

When we assume an unstable attitude of the body and attempt to regain balance by bringing a powerful set of museular movements into play to save ourselves from sudden precipitation, the effort is associated with a much greater sense of exertion than could be accounted for by the muscular energy used. It seems natural to assume that this exertion is the result of a purely voluntary act, whereas, without considering the fundamental characters of volition, we know that the act is more than probably the direct effect of reflex processes. *The character of the movements necessary to regain lost equilibrium is the same as that of forced movements which cause loss of balance in vertigo.* The reeling gait, unilateral deviation, falling forwards, backwards, or sideways, are all forced movements which occur in spontaneous vertigo.

### *Experimental Vertigo.*

The same movements can be reproduced in normal persons by certain physical stimuli, which unbalance the impression-complex: for instance, (1) by irrigating the ear with hot or with cool water, (2) by whirling quickly round and round, (3) by passing a transephalic current of galvanism, (4) by placing a prism before one eye, (5) by laterally displacing the globe of one eye by gentle pressure with the finger. The last mentioned is a well-known physiological experiment recently brought to mind in a paper by Hughlings Jackson and Paton (80).

*Experiment.* If we cover one eyeball and, while walking and looking straight ahead, displace the other eyeball laterally inwards by pressure with the finger at the outer canthus, we make objects in the visual field appear laterally displaced too. The retinal impressions and the oculo-motor impressions are out of harmony and a feeling of vertigo is produced, accompanied by lateral deviation in gait toward the direction of the displaced image. Sometimes this effect is more noticeable when the displaced eyeball is suddenly released, the deviation in this case being in the same direction as the retinal image moves in its return to the normal position. In trying the experiment an attempt should be made to walk straight to an object in view. The sensation of dizziness may last some minutes afterwards in some individuals, and is sometimes accompanied by slight nausea and headache.

We can reproduce still more typical forms of vertigo with all the varied characters of the spontaneous forms by stimulating the vestibular labyrinth (11, 22, 27, 38, 45, 50, 93, 98, 99, 122, 133, 135).

*Clinical Vertigo.*

As we have already mentioned, Gowers (58) maintained over twenty years ago that labyrinthine vertigo was by far the commonest of the clinical varieties.

*Mal de mer.* It is recognized that sea-sickness is a form of vertigo due to commotion set up in the semicircular canals. Patients whose labyrinthine reactions are brisk are much more liable than others to suffer sea-sickness, whereas those whose labyrinths are sluggish or absent, as in many deaf-mutes, do not experience sea-sickness (81). It is interesting to observe that nausea and vomiting are more likely to result from hyperstimulation of the superior canals than of the other two canals; this accords with the well-known fact that a rolling boat is more like to upset a sensitive subject than a pitching boat, and that one of the best means of diminishing or preventing *mal de mer* is to assume a reclining position athwart the vessel, with face uppermost. Some persons find relief by closing the eyes, thus removing an additional source of discordant impression.

*Ocular vertigo.* Vertigo purely ocular in origin may be experienced while watching an unfamiliar expansive mass in a state of continuous motion (81), such as a waterfall. Fleeting retinal images successively alternating with ocular 'movements of pursuit' produce a 'nystagmic demeanour' (James) and, being unaccompanied by familiar muscle-sense impressions, account for the instability and giddiness which continue after the eyes are turned aside, with the illusion that objects are now moving in the opposite direction (James).

*Train sickness* is another form of vertigo, which probably owes its origin in part to ocular and in part to labyrinthine disturbances. The giddiness associated with certain *intracranial lesions* may also be explained by disturbed *vestibular* or *ocular impressions*, or by interference with other co-ordinating impressions which such lesions induce (58).

So-called *laryngeal vertigo* does not appear to be associated with disordered ocular or vestibular impressions. The phenomenon is perhaps a form of temporary asphyxia due to laryngeal spasm. Several cases have been recorded during the last few years, including those by St.-Clair Thomson (150), Jobson Horne (78), and Whalen (160 a).

*Idiopathic epileptic* seizures frequently begin with a feeling of giddiness and sometimes definite rotatory vertigo. Gowers mentions the occurrence of giddiness in one-sixth of all attacks (58).

Some difficulty may be experienced in differentiating labyrinthine vertigo from vertigo associated with *petit mal*, particularly when the patient is the subject both of epilepsy and of gross disease of the ear.

Aldren Turner (151), in his monograph 'Epilepsy', makes a comparison between 'minor epilepsy' and 'minor aural vertigo'. In both conditions the onset of vertigo is sudden, the duration is brief, and the attack may be accompanied by pallor, loss of balance, confusion or possibly momentary blurring or

loss of consciousness. Tinnitus occurs in both diseases, but deafness would be in favour of aural vertigo. On the other hand, the occurrence of interparoxysmal dementia or amnesia, as well as of post-paroxysmal automatism, is absolutely characteristic of epilepsy.

An examination of the labyrinthine reactions should settle the diagnosis as a rule in a doubtful case.

*Other causes of vertigo.* Vertigo also occurs in malaria (47, 52) apart from treatment by quinine, as well as in other diseases such as pellagra (130) and Gerlier's disease (107) or paralyzing vertigo. Precisely how the infection in these diseases produces giddiness or which set of impressions is disturbed does not seem to be yet known.

Certain drugs are capable of setting up vertigo, especially alcohol, quinine, salicylates, tobacco, and probably a number of at present unknown toxins. Veronal and allied preparations may also produce vertigo.

*Hyperarterial tension.* Giddiness is not an uncommon symptom in *general diseases of the vascular system*, particularly when these are accompanied by arterial hypertension. Experiments on this subject have been undertaken by Lafite-Dupont (84), who found that a rise of arterial pressure was accompanied by a rise in pressure of the cerebro-spinal fluid, and also of the intralabyrinthine fluid. The same observer thinks that arterial high tension will explain certain auditory phenomena which he regards as due to a form of labyrinthine hyperaesthesia, and accounts for (1) tinnitus, (2) loss of appreciation for high tones, (3) diminution of sensitiveness to sound by bone-conduction, and (4) vertigo. It would seem, also, that certain forms of headache and otalgia are also explainable by the increased tension. Here we see the rationale of lumbar puncture (8, 9) for the relief of vertigo when associated with cerebro-spinal hypertension; also why we seek the cause by directing attention to the arterial system (116, 109).

*Vertigo and Vomiting.* Giddiness, tinnitus, and deafness represent a frequently-met-with clinical triad. The occurrence of vomiting as an outstanding feature in association with giddiness formerly gave rise to the conception of a gastric form of vertigo (Trousseau), anent which Gowers (58) in 1888 wrote, 'I do not think it is quite certain that there is such a thing as definite vertigo of purely gastric origin.' Gowers (58) has drawn a picture of the widely-spread erroneous belief that 'giddiness is due simply to biliousness'. He says, 'After severe vertigo has lasted for a short time, nausea comes on followed by vomiting, the patient becomes pale, and a cold sweat breaks out. The pallor and physical depression are often extreme and very alarming in aspect. If the giddiness persists the vomiting may go on for some hours, and after the stomach has been emptied bile is brought up, as is usual in continued vomiting. . . . *The vertigo is often increased by any movement of the head, and the patient may be unable to raise the head from the pillow without being sick.* The interference with the functions of the stomach occasions some indigestion, and especially some diarrhoea.'

The relation of vertigo and dyspepsia has recently been discussed by

F. Raymond (126). This writer asserts that dyspeptic symptoms do not precede the vertigo and cannot be regarded as a cause. He thinks it is especially important to examine and test the ears of patients suffering from dyspepsia and giddiness.

In spite of these authorities a belief still prevails that vertigo is due to derangements of the alimentary tract *per se*, and to this want of recognition of Gowers's teaching we must attribute the fact that we meet with patients suffering from gross disease of the labyrinth who have been treated for 'biliousness', 'gastric influenza', and 'fainting attacks due to dyspepsia', &c. Gowers (58) based his opinion on '106 consecutive cases in which vertigo made the patient seek advice, in no less than 94 of whom ear-symptoms were present—tinnitus or deafness or more often both'. He found that in '*all* his cases' there was 'diminution of appreciation for sound by means of bone-conduction'.

Now it is by no means certain that all cases of aural vertigo are due to morbid processes of the labyrinth, or of the auditory nerve, but that temporary affections of the external or middle ear by physical effects on the labyrinth may determine vertigo. Gowers makes it clear, therefore, that he excludes many cases of aural vertigo, which are associated with affections of the external or middle ear, characterized by deafness of the middle-ear type, when he says, 'a defect of hearing through the bone always existed, and in almost all cases in which it was sought a distinct difference between the two sides emphasized its pathological character.'

We are satisfied, therefore, that this authority did not over-estimate the frequency of aural vertigo. MacBride (96) observed a case of vertigo associated with so-called diminished intra-tympanic pressure, in which the symptoms of giddiness were instantly relieved by inflation of the middle ear. This case was commented upon by Grainger Stewart in 1884.

Dundas Grant (60) rightly insists on the fact that such cases are not uncommon in aural practice. In their well-known Textbook on Medicine, Fagge and Pye-Smith (46) quoted Knapp and Brünner (Zurich), who had described such cases, which are now better recognized than formerly. Examples of vertigo relieved by removal of impacted cerumen which pressed upon the tympanic membrane or ossicles were familiar to Toynbee (150).

Nor do Gowers's statistics take into account cases of vertigo due to infections of the labyrinth, consecutive to middle-ear disease, and which represent no inconsiderable class, judging by the frequency with which they are met with in aural practice (71, 88, 105, 134, 159).

### *Ménière: a Retrospect.*

When Ménière (103) fifty years ago drew attention to the association of vertigo with derangements of the ear, he had in mind the discoveries of Flourens (49) (1828-1842) demonstrating the relations of the semicircular canals to the sense of equilibrium. Ménière no doubt considered that Flourens's physiological data were applicable to the consideration of certain forms of giddiness and disturb-



ances of equilibrium which formerly had been regarded as due to a central cause. What he really showed was that sudden apoplctiform seizures, associated with tinnitus in persons previously healthy, may be followed by deafness, and that the cause of such attacks may be proved to be associated with an affection of the internal ear or labyrinth. The first nine cases Ménière brought forward were examples of paroxysmal vertigo, with tinnitus and deafness, unassociated with evidence of middle-ear disease. The tenth case was somewhat different from the others, and was the only one which ended fatally.

Briefly, this often-quoted case was that of a young woman who was seized with a severe cold, followed by deafness, and intense vertigo. *The vertigo was aggravated by the slightest movement of the head*, which brought on attacks of vomiting. The patient suffered from pains in the head, became comatose, and died on the fifth day of the illness.

*Post mortem.* Ménière examined the brain and internal ears. 'J'enlevai les temporaux afin de rechercher avec soin quelle pouvait être la cause de cette surdité complète survenue si rapidement. Je trouvai pour toute lésion les canaux demi-circulaires remplis d'une matière rouge, plastique, sorte d'exsudation sanguine, dont on apercevait à peine quelques traces dans le vestibule, et qui n'existait pas dans le limaçon' (cochlea).

Ménière does not explain the cause of death: 'La nécropsie démontra que le cerveau, le cervelet (cerebellum) et le cordon rachidien étaient absolument exempts de toute altération.' Nor did he show the true nature of the disease. He succeeded, however, in establishing an 'essential correlation between deafness, vertigo, and a lesion of the semicircular canal apparatus' in this patient.

Other writers than Ménière have shown a disposition (e.g. Cuvillier, 37) to attribute the lesion in this case to haemorrhage into the labyrinth, and there is a tendency to regard 'Ménière's disease and labyrinthine haemorrhage' as a clinical and pathological entity. The misuse of the term 'Ménière's disease' has been already pointed out by several writers, including W. A. Syme (147) (Edinburgh).

From our own experience the blood-stained effusion into the labyrinth was most likely the result, not of haemorrhage, but of an inflammatory exudate. The appearances as described by Ménière were similar to those seen in cases of acute (streptococcal) infections of the labyrinth secondary to middle-ear disease (134). The course of the symptoms and of the illness in Ménière's case is also consistent with the view that the onset of coma and death on the fifth day were due to increased intracranial pressure, caused by acute internal hydrocephalus (meningitis serosa maligna), which even Ménière may have regarded as an unessential feature. A parallel case was under the present writer's observation (136) in 1907;<sup>2</sup> death took place on the eighth day.

The statement by Ménière that the brain appeared normal does not belie this view, nor does the absence of any report concerning the middle ear. Ex-

<sup>2</sup> Compare also cases of serous meningitis by Ballance, Hinsberg, &c.

amples of intracranial infections due to acute otitis media unassociated with discharge from the ear are met with from time to time (134).

Cases similar to Ménière's tenth case would not necessarily prove fatal at the present time. By early incision of the membrane in acute non-perforative otitis media (French Congress of Otology), or by drainage through the antrum direct, the infection need not spread to the internal ear; and in cases in which the labyrinth is already implicated, and perhaps already associated with increased cerebro-spinal fluid, life may be saved by means of a properly conducted operation to remove the focus of infection, and to drain the labyrinth and meninges (160).

In upholding the view that Ménière's fatal case was due to infective processes we should mention that Alexander (4), according to J. S. Fraser (23), accepts the haemorrhagic hypothesis, and considers the case was one of splenic leukaemia. In one of Alexander's cases the right auditory and facial nerves were infiltrated in addition to extensive haemorrhage into both labyrinths. That true haemorrhage into the labyrinth may occur Alexander (4) has clearly shown, and we have in our literature records of this condition (110, 85, 157). But we cannot regard labyrinthine haemorrhage as the principal cause of the symptom-complex in the recurrent form of paroxysmal vertigo so frequently met with.

To what then are we to attribute the disturbances in the labyrinth in recurrent cases of vertigo? Pathological evidence is still scanty on this point, but there is a tendency to make primary degenerative processes in the vestibular nerve responsible for some of the cases (Manasse, 100); vaso-motor disturbances may account for others, while a considerable number are undoubtedly explained by diminution of the blood supply to the labyrinth due to diseases of the basilar and internal auditory arteries or to general vascular disorder (116). See Friedreich's (55) case.

Labyrinthine hyperaemia may develop in the course of acute otitis media, and is also caused by such drugs as amyl nitrite. Albert Gray (161) lays stress on vaso-motor disturbances.

It is possible that certain toxins are responsible for more cases than we are at present aware of.

One of the most illuminating monographs on this subject is that by L. V. Frankl-Hochwart (72). This writer's observations are based upon records of 208 patients who presented the Ménière symptom-complex and who were carefully examined by competent otologists.

### *Examination of labyrinth.*

It may be profitable to briefly consider here the methods of investigating the functions of the labyrinth (11, 19, 163).

The vestibular nerve, which conveys impressions from the semicircular canals, utricle, and saccule, is stimulated normally by ordinary movements of the head, and may be hyperstimulated by (1) irrigation of the ear with hot or with cold

water; (2) by whirling round and round and coming to a sudden stop; (3) by galvanism applied to the ear; by meatal compression or rarefaction in certain cases, especially when middle-ear disease and labyrinthine fistula coexist.<sup>3</sup>

The functional examination of the special apparatus for preserving equilibrium is necessary to ascertain (1) whether the apparatus is normal, (2) whether it is defunct, (3) whether it is partially defective.

The clinical methods of examination are based upon the results of physiological researches into the labyrinth in the seventies of last century, especially by Mach (98), Breuer (22), Cyon (38), which have been followed by the studies of Ewald (45), von Stein (143), Högyes (73), and Bárány (11). Their researches have been confirmed by numerous other independent investigators (93, 99, 133, 152).

*Forced movements due to labyrinthine stimuli.—Experimental Rombergism.* The type of movement obtained in normal persons depends upon the part of the labyrinth excited. If one superior semicircular canal is hyperstimulated the subject falls over sideways when the head is erect. Irrigation of the right ear alone with hot water (105° to 115° F.) (assuming the head to be erect) will produce a fall towards the left side of the head; cool water a fall to the right side: irrigation of the left ear alone produces corresponding effect. Disagreeable sensations may be set up if unnecessarily strong stimulation is applied.

By whirling we can pick out each semicircular canal to stimulate it by suitably adjusting the position of the head in respect to the plane of rotation. In this way forced circus-movements, lateral deviation, pleurothonia, opisthonia, and emprosthonia can each be provoked at will, both in normal subjects and in those who possess only one set of semicircular canals. In patients whose semicircular canals (on both sides) cease to functionate it is impossible to produce these forced movements or vertigo by the methods mentioned (86, 98, 122, 135).

*Forced movements of the eyeball: Deviation: Nystagmus.* Hyperstimulation of the labyrinth produces deviation of the eyes, in a direction which corresponds to that of the head- and body-movements. The eye-movements are sometimes the first forced movements noticed; sometimes the movements of the head and trunk are first observable. Nystagmus comes into play as the result of a secondary reflex, due perhaps to muscle-sense impressions, but especially easily produced by attentive deviation of the eyes in the direction opposite that of the primary deviation.

Spontaneous vertigo is, during the paroxysmal stage, usually accompanied by nystagmus, as described by Hughlings Jackson and others (83).

*Nystagmus and vertigo.* It has been known for more than 100 years (39) that nystagmus could be produced by rotation. In 1828 Flourens noticed

\* Experience is necessary in the application of these tests. No definite rules can be laid down as to the temperature necessary for a reaction in individual subjects; nor the angular velocity and number of revolutions which may be required. It is always advisable to find the minimum stimulus to produce a definite reaction. Minimal stimuli in some diseases, e.g. Friedreich's ataxia, may cause almost general convulsive reaction: great care is therefore to be exercised.

nystagmus as the result of interference with the vestibular labyrinth (49). It is only comparatively recently that attention has been concentrated clinically upon the type of nystagmus associated with labyrinthine vertigo (11, 133).

We recognize a particular kind of nystagmus of which there are three main types, namely, rotary, horizontal, and vertical (rarely oblique). Labyrinthine nystagmus is most intense when the visual axes are directed to a certain point of the binocular field (the point of maximum intensity). The to-and-fro movements are alternately unequal in velocity, the more rapid movement being towards the point of maximum intensity. Nystagmus, which exists only when the visual axes are directed beyond the limits of the binocular field, cannot be regarded as labyrinthine in origin, even though it resemble this form in type.

*One of the chief characteristics of labyrinthine nystagmus is, that it is asymmetrical.* But all forms of nystagmus which have this quality are not labyrinthine in origin. Some are purely ocular; some are congenital. Labyrinthine nystagmus tends to decrease in intensity in the course of time (15).

(1) When labyrinthine nystagmus or other forced movements result from stimuli applied to the semicircular canal apparatus, we infer an intact membranous labyrinth and vestibular nerve.

(2) Imperfect reactions indicate partial defects.

(3) When stimuli are inert, we infer that either the labyrinth or vestibular nerve is defunct.

(4) Spontaneous labyrinthine nystagmus may be modified, or other forced movements inhibited or induced by stimulation of a partly functioning labyrinth or vestibular nerve.

(5) Failure to produce any effect on existing spontaneous labyrinthine nystagmus, or to set up any new forced movements by different forms of stimulation applied to the semicircular canals or vestibular nerve, proclaims a defunct organ or nerve.

The following tables summarize the principal conditions under which it is possible to observe the various kinds of labyrinthine nystagmus (133).

TABLE I. *Rotatory (counterclockwise) Nystagmus observable during attentive deviation and fixation of the eyeballs to the right.*

(1) By thermal methods.

Cold water irrigation	Left ear	Head erect
Hot " "	Right "	" "
" " "	Left "	" inverted
Cold " "	Right "	" "

(2) By whirling about a vertical axis.

Direction of whirling counterclockwise	Face downwards
" " " clockwise	" upwards

(3) By galvanism.

Current of 5 to 15 milliamperes	Kathode to right ear, anode in right hand
" " "	Anode to left ear, kathode in left hand

TABLE II. *Clockwise Nystagmus observable during attentive deviation and fixation of the eyeballs to the left.*

## 1) By thermal methods.

Cold water irrigation	Right ear	Head erect
Hot " "	Left "	" "
" " "	Right "	" inverted
Cold " "	Left "	" "

## (2) By whirling about a vertical axis.

Direction clockwise	Face downwards
" counterclockwise	" upwards

## (3) By galvanism.

Current of 5 to 15 milliamperes	Kathode to left ear, anode in left hand
" " "	Anode to right ear, kathode in right hand

TABLE III. *Horizontal Nystagmus observable during attentive deviation and fixation of the eyeballs to the right.*

## (1) By thermal methods.

Cold water irrigation	Right ear	Face downwards
Hot " "	Left "	" "
" " "	Right "	" upwards
Cold " "	Left "	" "

## (2) By whirling about a vertical axis.

Direction counterclockwise	Head erect
" clockwise	" inverted

(3) By pressure on a fistula of the right horizontal semicircular canal in certain cases of middle-ear disease.

TABLE IV. *Horizontal Nystagmus observable during attentive deviation and fixation of the eyeballs to the left.*

## (1) By thermal methods.

Cold water irrigation	Left ear	Face downwards
Hot " "	Right "	" "
" " "	Left "	" upwards
Cold " "	Right "	" "

## (2) By whirling about a vertical axis.

Direction clockwise	Head erect
" counterclockwise	" inverted

(3) By pressure on a fistula of the left horizontal semicircular canal in certain cases of middle-ear disease.

TABLE V. *Vertical Nystagmus observable during attentive deviation of the eyeballs upwards (in relation to the orbit).*

## (1) By whirling.

Counterclockwise	Head with right side downwards
Clockwise	" " left " "

TABLE VI. *Vertical Nystagmus observable during attentive deviation and fixation of the eyeballs downwards.*

(1) By whirling.

Clockwise	Right side of head downwards
Counterclockwise	Left " " "

Buys and Hennobert (27) have succeeded in recording tracings of the eye-movement in labyrinthine nystagmus by an adaptation of Mayer's tambour applied to the globe of the eye, the tracing being taken in the usual way by means of a stylot and revolving drum.

It is possible to photograph these eye-movements and reproduce the movements cinematographically, as the present writer (137) has done.

The phenomena of nystagmus may be associated with the symptom-complex of Ménière's vertigo, as Hughlings Jackson observed many years ago (80).

The degree of nystagmus produced by the above methods in normal subjects does not always correspond to the intensity of the vertigo. In the majority of individuals nystagmus and vertigo correspond, but there are exceptions; first, of those who become giddy before nystagmus develops; and, secondly, those who exhibit well-marked nystagmus in response to hyperstimulation without experiencing sensations of giddiness. It is, however, worth noticing that patients who display nystagmus in response to stimulation, without evincing any sign of giddiness, appear to take some pains to *immobilize the head*. It is evident that nystagmus does not play the part of a causal factor in giddiness any more than ataxic gait would do, and yet it is possible by closing the eyes in one case and by resting in the other that the feelings of giddiness are somewhat diminished. The same relationship between nystagmus and vertigo holds good in spontaneous seizures (93, 95).

*New Tests (Bárány, 1910).* We shall conclude this consideration of the functional reactions of the semicircular canal apparatus by referring to a certain form of forced movement which has been introduced recently by Bárány (14) and is of interest in connexion with the investigation of cerebellar functions (129). If, during a state of labyrinthine excitation artificially induced, a normal individual attempt to execute certain purposeful movements it will be observed that the intended movements are modified according to the particular stimulus applied.

When, for instance, a normal subject who is seated in a chair which is rotated a certain number of times and then stopped immediately attempts to point with the finger to a fixed object hidden from view in front of him, he will deviate his finger several inches to one side, just as he will deviate in his gait to one side (circuswise) if he attempts to walk forwards with eyes closed immediately after rotation.

This deviation of the pointing hand is to be regarded as a normal reflex act, due to hyperstimulation of the horizontal semicircular canals. Either hand will

behave in the same way. The direction of deviation is the same as that of rotation.

In cases of unilateral destructive lesion in one cerebellar hemisphere the normal deviation of the finger is not produced in the ipsilateral limb when the chair is turned to the contralateral side, whereas after rotation to the ipsilateral side the normal deviation reaction takes place in the limbs on both sides.

Such is a somewhat concise statement of the reaction which Bárány demonstrated correctly in three unselected cases of unilateral cerebellar lesion; the patients had recovered, after a tumour or cyst had been removed by Horsley from the lateral lobe of the cerebellum, some months or years previously. The present writer has since obtained corroborative evidence; but we have yet to learn whether we can place these reactions side by side with those described by Grainger Stewart and Gordon Holmes (75).

#### *Cases Clinically and Pathologically Examined.*

The number of cases in which careful clinical examination of the special reactions of the labyrinth have been compared with detailed histological examination is still so few, that a case published by Alexander Bruce and J. S. Fraser (23) is of special interest.

Alagna (2) (de Palerne) has written an important paper on 'Tumours of the Auditory Nerve', in which he has compiled some twenty cases collected from continental literature from 1840 to 1909. This writer restricts his study to cases of tumour originating in the auditory nerve as distinct from those which arise in the dura mater of the internal auditory meatus or from the posterior surface of the petrous bone. The symptoms noticed in these cases were (1) *labyrinthine*, namely giddiness, ataxia, tinnitus, deafness, vomiting; and later (2) *intracranial*, e.g. headache, followed by signs of involvement of other cranial nerves, especially from the fifth to the tenth.

Voltolini's (154) case (1861) appears to have been the first in which the pathological examination was made histologically. A sarcoma was found involving the seventh and eighth nerves in the internal auditory meatus.

Brückner's (24) case (1867) was typical. A woman of 28 years had suffered from deafness in the left ear with vertigo, which lasted four years before other nerves became involved. Autopsy:—glioma involving sixth to tenth nerves on the left side.

Sorgs's (141) case (reported in 1901 from Schroetter's clinic) is one of the first in Alagna's (2) list which gives a report of an otological examination which was made by Alt:

A woman, aged 42, for eighteen months vertigo and weakness of limbs, followed by vomiting and headache; gait deviating to the right; defective hearing on the left side; diplopia; hyperaesthesia of scalp; tremor of limbs; fixed pupils;

sixth nerve paralysis (left); horizontal nystagmus; Rombergism; weakness of left limbs; no sensory disturbances of extremities; taste, slow reaction; tachycardia; knee-jerks brisk; fifth nerve neuralgia (left); visual hallucinations; hearing, right side normal.

Weber's test referred to the right. Left side: Rinne, positive (= air better than bone conduction); Schwabach's test, negative (= loss of bone conduction); Eustachian tube patent; no improvement by inflation. Autopsy: fibro-glioma of left auditory nerve.

Alexander and Frankl-Hochwart (72) also give the results of a special examination.

A man, aged 49, whose gait became uncertain two years before he was seen, had vertigo and fell; there was frequent vomiting. He suffered from noises in the ears, deafness, and headache. Nystagmus was evident on deviation upwards and to either side. The pupils reacted to accommodation but not to light. The fifth cranial nerve was involved. Alexander's examination of the ears showed the tympanic membranes were both opaque. The voice was heard 5 metres from right ear and 1 metre from the left.

<i>Right.</i>		<i>Left.</i>
Opaque	Tympanic membranes	Opaque
5 metres	Voice	1 metre
Not on contact	Watch	Not on contact
Great loss	High tones	Great loss
Slight loss	Low tones	Slight loss
Referred to right	Weber	—
Positive	Rinne	Positive (air better than bone conduction)
Negative	Schwabach	Negative (loss of bone conduction)
Slight improvement	Eustachian catheter	No improvement

Before death facial paralysis was observed, and the patient succumbed in a state of coma which followed the intense headache and frequent vomiting from which he suffered.

Autopsy (by Dr. Landsteiner). Extreme hydrocephaly; tumour of left seventh and eighth nerves. Histology of the labyrinth showed atrophic degeneration of cochlear nerve, ganglia, organ of Corti, stria vascularis, &c.

A systematic examination of the hearing is necessary before we can localize a defect. Slight imperfections in hearing may be undiscovered if we trust to too rough and ready methods. As we owe most to Bezold's system, it may be advantageous to recall his methods. Hearing distance for whispered numbers is first tried. Then the hearing is tested with one of the lower middle tuning-forks by air and by bone; next the original Rinne and Weber tests are applied. These must be repeated several times, and any discrepancies noted for further investigation. The acuity of hearing high tones is determined with one of the high forks, e.g. c<sup>5</sup>. Lastly, we ascertain the limits of the range in the upper and lower scales. When the range is small



and the loss of acuity very great we determine the presence or absence of 'hearing reliefs (19)'.

The diagnosis of an affection of the sound-perceiving apparatus depends upon the following points: (1) relatively good perception for deep tones; (2) decidedly poorer perception for high tones; (3) a low lower-tone limit; (4) marked contraction of the upper range; (5) diminution of acuity for tuning-forks by bone conduction and Rinne's reaction, positive (air much better than bone conduction).

The present writer has, however, observed cases of gross disease of the auditory nerve (tumour) in which there was a rapid progressive loss of low tones which attained a loss of nearly  $4\frac{1}{2}$  octaves (on the side of the lesion), while the highest tones were accurately and consistently preserved on both sides; moreover, Rinne's test, which was at first positive, became negative. The patient, a woman (Mrs. H. C.), died in the National Hospital for the Paralysed and Epileptic. The last examination was made the day before she succumbed, and the autopsy took place a few hours after death. The middle ear and stapes were perfectly normal. A tumour involved the left auditory nerve, the examination of which is unfinished (Nov., 1910).

In other cases of auditory nerve tumours, a general contraction of the auditory field has been observed. Those, therefore, who are accustomed to rely upon a single tuning-fork for a diagnosis will do well to keep in mind that unilateral Rinne negative does not exclude a nerve lesion, while a positive Rinne may be 'relatively negative' and does not exclude a middle-ear defect (cf. current otological literature).

Lastly, diminished bone conduction may be restored in certain cases of Eustachian obstruction to normal bone conduction by simply inflating the Eustachian tubes, which shows that loss of bone conduction does not necessarily indicate auditory nerve disease. This point does not generally appear to have been noticed.

Auditory symptoms, namely tinnitus, defective hearing, and vertigo, were among the early symptoms of all Stewart (145) and Holmes's eleven cases (not included in Alagna's paper) of extra-cerebellar tumour at the National Hospital, Queen Square, while deafness or tinnitus was absent in only a few of the intra-cerebellar cases.

The following appear to have been unusual<sup>4</sup>:—

*Case I.* Large tubercular tumour of left lateral lobe, the greater part of which was destroyed. 'There was no deafness, tinnitus, or vertigo', but the patient had had 'fainting attacks with falling backwards'.

*Case VIII.* Glioma of vermis and adjacent parts of each lateral lobe, chiefly of the right. (Recovered after removal of tumour by operation.) The patient had 'vertigo and tinnitus like ringing bells, but no deafness'.

*Case IX.* A similar case, but in which there was defective hearing on one side.

<sup>4</sup> *Brain*, p. 559, part 108.

*Case X.* Glioma of vermis and lateral lobes, chiefly right. 'Never vertigo, tinnitus, or deafness.'

According to these authors' evidence it would seem that the clinical triad, vertigo, tinnitus, and deafness, is consistently met with in auditory nerve tumours, and occasionally in tumours of the vermis or lateral hemisphere of the cerebellum.

The presentation of atypical signs in auditory nerve tumours is recorded in a case by H. Oppenheim (114), in which homolateral spastic paresis, and analgesia, clonus, and Babinski extensor response were associated with the usual signs of a left cerebello-pontine tumour (confirmed by autopsy).<sup>5</sup>

The absence of characteristic signs is also recorded by F. Schupfer (132).

The importance of contrasting the symptomatology of cerebellar and labyrinth disorders is emphasized by the parallelism which we find between diseases of the labyrinth and extra-cerebellar tumours on the one hand, and between cerebellar abscess and cerebellar tumours on the other (129).

In Neumann's monograph, *Otitic Cerebellar Abscess*, conclusions are based on 196 cases of otitic cerebellar abscess and 336 cases of otitic temporo-sphenoidal abscess (112).

The labyrinth was first diseased in the majority of cases of cerebellar abscess due to chronic ear disease.

Acute otitis media accounted for 12 per cent. of the cerebellar abscesses. The path of infection was direct from the antrum or through the lateral sinus to the cerebellum, not through the labyrinth in these acute cases.

The present writer noticed the formation of an intracerebellar abscess (left side), unaccompanied by giddiness, in a patient whose left labyrinth had previously become disorganized (133). Inco-ordination, paroxysmal yawning, and nystagmus 'towards the lesion' were the most noteworthy signs, with absence of labyrinth reactions. Another patient (133) had headache, vertigo, falling backwards, with inco-ordination of upper extremities, hypotonia of the left limbs, and dysdiadokokinesia and coarse lateral nystagmus 'to the left', with tendency to deviate eyes to the right. There was a retrocerebellar (extra-cerebellar intradural) abscess, with inflammatory oedema of the left lateral lobe.<sup>6</sup>

The importance surgically of a correct diagnosis of cerebellar lesion is emphasized by R. T. Williamson, who has compiled some statistics on the results of cerebellar surgery (161; see also 10, 21, 70, 94, 164).

### *Principles of Treatment.*

Vertigo is rarely mono-symptomatic; other symptoms are generally though not invariably present. The first step is to seek the malady of which the

<sup>5</sup> See 'Zur Lehre vom Kleinhirnbrückenwinkeltumor', *Neurol. Centralbl.*, Ap. 1, 1910, p. 338; abst. Edwin Bramwell, *Rev. of Neurol. and Psych.*, 1910, viii, 51, p. 309.

<sup>6</sup> *Proc. Roy. Soc. Med. (Otol. Sect.)*, iv.

vertigo is the effect. Seeing that in over 90 per cent. of cases (Gowers) the disturbance is in the labyrinth, attention is first directed to the ear. It is necessary therefore to inspect the tympanic membrane, though this is more often normal than otherwise; the middle ear, when the membrane is defective; the naso-pharynx and Eustachian tubes, which may be choked.

We often require to make a searching test of the hearing and vestibular sense organs. As aids to diagnosis an examination of the eyes and a general neurological survey must not be omitted. In certain cases particular care is called for lest signs of an intracranial affection be overlooked—for instance, when due to involvement of the projection fibres of the vestibular nerve. In cases in which the labyrinthine functions are normal the cause of the vertigo must be referred to a possible ocular defect as the next most likely cause. The examination of the eyes will be directed to the field and acuity of vision, accommodation, ocular muscle balance. To reveal certain ocular pareses special methods are required. The importance of optic neuritis need only be mentioned.

The completion of the neurological examination has been dealt with in excellent treatises on diseases of the nervous system, by writers especially qualified to speak from first-hand knowledge and experience. In seeking for a possible syphilitic virus, Wassermann's reaction proves of service. In other cases it will be necessary to test the blood pressure and its variability, also the cerebrospinal fluid pressure, and its chemical and cellular contents. Without thorough examination assignable causes may be overlooked or misunderstood (31, 142, 162). Vascular, renal, and digestive functions may be at fault in connexion with defective metabolic processes, which may be responsible for the circulation of chemical or other toxins or disturbers of vaso-motor action.

### *Summary.*

Vertigo—a state of consciousness of the effect on motor centres of a want of harmony between afferent impressions.

Chief afferent impressions disturbed :

1. Labyrinthine (vestibular).
2. Ocular.
3. Muscular sense (including ocular).

Clinical vertigo—due to vestibular nerve disorders in over 90 per cent. of patients who complain of giddiness (cf. Gowers).

Less common causes of vertigo—ocular, which comes next in order of frequency, and lastly the important group due to cerebellar, medullary, and pontine disturbances, and other intracranial affections.

Symptoms of vertigo :

Subjective of self.

Subjective of surroundings.

Forced movements.

Vomiting.

Nausea.

Pallor.

Faintness.

Depression.

Concentration of attention upon distressing sensations.

Blurring of consciousness (rare).

Associated :

Tinnitus.

Defective hearing.

Visual sensations.

Headache.

When the vertigo accompanies an intracranial lesion with increased intracranial pressure, there will be—headache, optic neuritis (see Paton), and interference with the function of other cranial nerves besides the second and eighth.

Signs formerly regarded as purely cerebellar are now known to be evoked by labyrinthine lesions also.

e. g. 1. 'Cerebellar attitude of head' may be 'vestibular attitude' (Horsley).

2. Gait: locomotor inco-ordination—cerebellar and vestibular almost identical in many respects,

3. Hypotonia ipsolateral.

4. Rombergism.

Signs which are not labyrinthine:

1. Dysdiadokokinesia (Babinski).

2. Non-locomotor inco-ordination, e. g. the familiar 'finger to nose' test.

3. Asynergia (Babinski).

As regards the pathological processes in the vestibular nerve endings, there is ample evidence of (1) infective lesions, usually secondary to middle-ear infection; (2) haemorrhage (labyrinthine or vestibular nerve); (3) auditory nerve tumours, which play a definite part. And yet there is a large percentage of cases of well-defined labyrinthine type of vertigo associated with permanent auditory defects in which the nature of the lesion is indefinite.

In some of these, ganglionic degenerations have been observed by Manasse (100) and other otological histologists. In others calcareous deposits have been discovered in the labyrinth (61). And there still remain examples in which the lesion is not disclosed by the ordinary methods of examination.

Possibly some vertigos are the result of toxic substances, acting directly on the nerve tissues or indirectly by causing unilateral arterio-spasm or vasodilation. Here then is a field for fruitful research, which can only be filled by consideration of all possible data obtainable.

## REFERENCES

1. Achard (see Debove and Achard).
2. Alagna, *Archives internat. de Laryngol., d'Otol. et de Rhinol.*, 1909.
3. Alessi, U. (De Sassari), *Rivista italiana di neuro-pathologia, psichiatria ed elettroterapia*, 1908, i. 324.
4. Alexander, Gustav, *Zeitschr. f. Heilkunde*, 1906.
5. Alexander and Frankl-Hochwart (see Hochwart).
6. Anton, *Arch. f. Ohrenheilk.*, 1896, xli (quoted by Alagna, q. v.).
7. Armour, Donald. Case of successful division of auditory nerve, cited by Yearsley, *Text-book of Diseases of the Ear*, 1909, 346.
8. Babinski, *Journ. de Méd. et de Chir. pratiques*, 1908.
9. Babinski, quoted by Hunter Tod, *Med. Ann.*, 1905, 245.
10. Ballance, C. A., *Trans. Otol. Soc. U. K.*, 1904, 67; *Some points in the Surgery of the Brain*, Lond., 1908.
11. Bárány, Robert, *Physiologie und Pathologie des Bogengangapparates*, F. Benticke, Wien und Leipzig, 1907.
12. Bárány, Robert, *Internat. Zentralbl. für Ohrenheilkunde*, 1908, viii, Heft 1 und 2, Bibliography (209 ref.).
13. Bárány, Robert, *Rev. of Neurol. and Psych.*, Edin., 1909, vii. 295 (abst. J. S. Fraser).
14. Bárány, Robert, Neurological Section, British Medical Association, London, 1910; *Brit. Med. Journ.*, 1910, ii. 1245.
15. Bárány, Robert, Otol. Sect., British Medical Association, London; *Brit. Med. Journ.*, 1910, ii. 1675.
16. Barr (see Carslaw).
17. Batten, F. E., concerning cerebellar attitude (quoted by Ballance, *loc. cit.*).
18. Batten, F. E., *Brain*, Lond., xxviii, 1905, 484.
19. Bezold, F., and Siebenmann, F., *Text-book of Otology* (trans. Holinger, J.), 1908.
20. Bonnier, P., *Le Vertige*, Paris, 1904.
21. Borchardt (quoted by Hildebrand, q. v.). Statistics based on 101 operations for cerebellar tumour, diagnosis corroborated 39, survived 22, improved or cured 17 (see Williamson); lateral recess tumours 30, survived 7, cured 4.
22. Breuer, *Anzeiger der k. k. Gesellschaft der Ärzte in Wien*, vii. 1873 (quoted by Bárány).
23. Bruce, Alexander, and Fraser, J. S., *Rev. of Neurol. and Psych.*, 1910; *Journ. of Laryngol., Rhinol. and Otol.*, 1910.
24. Brüchner (quoted by Alagna).
25. Brünner (quoted by Fagge and Pye-Smith).
26. Buchanan (see Carslaw).
27. Buys and Hennebert, *Arch. internat. de Laryngol., d'Otol. et de Rhinol.*, 1909, 1910.
28. Buzzard, Farquhar (see Wallace and Marriage).
29. Carslaw, *Glasgow Hospital Reports*, 1898, i. 93.
30. Charcot, *Ménière's Vertigo: Vertigo ab auro laesa*, New Sydenham Society, 1881 (trans. by Sigerson).
31. Chavigny et Schneider, *Bull. et Mém. de la Soc. méd. des hôp. de Paris*, 1909, xxviii. 68 (abstract by J. D. Rolleston, *Rev. neurol. et psych.*, 1909, vi. 610).
32. Chatle, Arthur, *Trans. Otol. Soc. U. K.*, 1904, v. 72; also *Arch. of Otology*, 1897, xxvi. 185.
33. Chèze, Gabriel, *Syndrôme du noyau de Deiter par hémorragie localisée de protubérance*, *Lyon. méd.*, 1708, cxi, 705.
34. Clarke, R. H., and Horsley, Sir Victor, *Brain*, 1905, xxviii. 13.
35. Crepuska (quoted by Alagna).
36. Cushing, *Journ. Amer. Med. Assoc.*, 1909, liii. 184 (abst. by C. H. Holmes, *Rev. of Neurol., &c.*, 1909, vii).
37. Cuvillier (see Debove and Achard).
38. Cyon, *Recherches expérimentales sur les fonctions des canaux semicirculaires*, 1879, 1880.
39. Darwin, *Zoonomia*, 1801.

40. Debove and Achard, *Man. de Méd.*, 551 et seq., 'Maladie de Ménière.'
41. Deganello, U., *Arch. ital. de Biol.*, Turin, 1905, xliv. 201-214.
42. Deganello, U., *Arch. ital. de Biol.*, Turin, 1906, xlv. 156-172.
43. Devaines, 1852 (see Gairdner).
44. Dreyfuss, *Zeitsch. für Ohrenheilkunde*, xlix. 343.
45. Ewald, *Physiologische Untersuchungen über das Endorgan des Nerv. octavus*, Wiesbaden, 1892.
46. Fagge and Pye-Smith, *Principles and Practice of Medicine*, 3rd ed., 767.
47. Ficacci, L., 'Syndrome méningo-cérébelleux dans la tierce printanière', *Soc. Lancisiana degli ospedali di Roma*, 5 janvier 1907 (*Rev. neur.*).
48. Fleischmann (see Alagna).
49. Flourens, *Mém. Acad. d. Sc. de l'Inst. de France*, Paris, 1828, ix. 5.
50. Flourens, *Recherches expérimentales sur les propriétés du système nerveux*, Paris, 1842.
51. Forli, V., 'Un cas de syndrome cérébelleux dû à la malaria,' *Soc. Lancisiana degli ospedali di Roma*, 5 gennaio 1907. (*Haemamoeba praecox sans association du parasite estivo-automnal.*) (*Rev. neur.*)
52. Förster, *Würzburg. med. Zeitschrift*, 1862 (quoted by Alagna). Malignant disease of labyrinth.
53. Fraser, J. S. (see Bruce and Fraser).
54. Fraser, Bárány, 'Critical Review,' *Rev. of Neurol. and Psychol.*
55. Friedreich, quoted by Gruber as being cited by Moos, *Klinik der Ohrenkrankheiten*, 1863 (embolism of internal auditory artery in case of endocarditis, sudden deafness accompanied by grave symptoms).
56. Gairdner, *Lancet*, Lond., 1861, i. 477.
57. Gibson (see Lake).
58. Gowers, Sir William, *Diseases of the Nervous System*, 1888, 725, 728, 733.
59. Gradenigo, *Il Morgagni*, 1907, xlix, nos. 10, 11, 593-624, 696-709.
60. Grant, Dundas, 'Discussion on Vertigo,' *Trans. Otol. Soc. U. K.*, 1905.
61. Gray, Albert A., *Text-book of Diseases of the Ear*, 1910.
62. Grenet (see Sergent and Grenet).
63. Guthrie, abst. review of Bárány, 'On Labyrinthine Nystagmus,' *Brain*, 1906, xxix. 383.
64. Halphen (see Lemaître and Halphen; also Lombard and Halphen).
65. Harris, *Proc. Roy. Soc. Med.*, Lond., 1910, ii; *Neurol. Sect.*, 81.
66. Hastings, H., *Arch. of Otol.*, New York, 1908, xxxvii. 558.
67. Hegener, *Beitr. z. Anat. etc. des Ohres*, ii, Heft 6 (abst. by J. S. Fraser, *Rev. neurol. et psychol.*, 1909, vii. 478).
68. Hennebert (see Buys and Hennebert).
69. Henschen, Folke (quoted by R. T. Williamson, q. v.), *Zeitsch. f. klin. Med.*, Berlin, 1907, lxiii. 115.
70. Hildebrand, *Deutsche med. Woch.*, 1909, xxxv. 1999 (quoted by Williamson, q. v.).
71. Hinsberg, V., *Arch. of Otology*, 1907.
72. Hochwart, *Nothnagel's Clinique*, 1904; 'Erfahrungen über Diagnose und Prognose des Ménièreschen Symptomenkomplexes,' *Jahrbücher für Psychiatrie und Neurologie*, 1905, xxv.
73. Högyes, *Archiv f. d. ges. Physiol.*, Bonn, 1881, xxvi. 558.
74. Holmes, C. H., see Moleen.
75. Holmes (see Stewart and Holmes).
76. Holmes, *Brain*, Lond., 1905, xxviii. 556.
77. Horne, *Proc. of Roy. Soc. of Med.*, Lond., 1909, ii. 2; *Laryngol. Sect.*, 105.
78. Horsley, Sir V., *Trans. Otol. Soc. U. K.*, 1905, v.; Cavendish Lecture, West London Hospital, 1909; Hughlings Jackson Lecture, 1907; *Brit. Med. Journ.*, 1907, i. 803.
79. Howell, *Proc. Roy. Soc. Med.*, Lond., 1910, *Neurol. Sect.*, iii. 2, 85.
80. Jackson and Paton, *Lancet*, Lond., 1909, i. 900; also Jackson, *Brain*, 1879-80, ii. 29.
81. James, W., *The Principles of Psychology*, ii. 79 et seq., 'Perception'; see also *Amer. Journ. Otol.*, IV.
82. Jones, E., *The Differential Diagnosis of Cerebellar Tumours*; Boston, *Med. and Surg. Journ.*, 1909, clxi. 281.
83. Kipp, *Trans. Amer. Otol. Soc.*, 1888.

84. Lafite-Dupont, *X<sup>me</sup> Congrès français de Méd.*, Genève, 1908, ii. 74.
85. Lake, R., *Diseases of the Ear*, 2nd ed. Microscope sections of the internal ear in case of leukaemia.
86. Lake, R., *Proc. Roy. Med. Chir. Soc.*, 1900, lxxxiii.
87. Lake, R., *Trans. Otol. Soc. U. K.*, 1904, iv. 69.
88. Lake, R., *Trans. Otol. Soc. U. K.*, 1905, vi. 60 (also see Yearsley).
89. Lake and Gibson, *Proc. Roy. Soc. Med.*, Lond., Otol. Sect., 1907-8, i. 3, 150.
90. Landsteiner (see Hochwart).
91. Lavoix (see Minet and Lavoix).
92. Lee, F. S., *Journ. of Physiol.*, Camb., 1894, xv. 311.
93. Lemaître, F., and Halphen, *Ann. des mal. de l'oreille, etc.*, xxxiv.
94. Lichtheim, *Deutsche med. Woch.*, 1905, xxxi (quoted by Williamson, q. v.).
95. Lombard and Halphen, *Prog. méd.*, xxiii.
96. MacBride, P., *Med.-Chir. Soc.*, Edin. 1881 (also quoted by Gowers, q. v.).
97. McDonnell, *Med.-Chir. Trans.*, Lond., 1875, lviii. 369-375.
98. Mach, *Grundlinien der Lehre von den Bewegungsempfindungen*, Leipzig, 1875.
99. McKenzie, *Journ. of Laryngol.*, Lond., 1909.
100. Manasse, *Zeitsch. f. Ohrenh.*, Wiesb., 1906, lii.
101. Marrassini, A., *Arch. ital. de Biol.*, 1907, xlvii. 135-176.
102. Marriage, *Trans. Otol. Soc. U. K.*, 1907, viii. 41 (see also Wallace and Marriage).
103. Ménière, *Gaz. méd. de Paris*, 1861, 88, 239, 379, 597.
104. Meyer, *Neurol. Centralbl.*, Leipz., 1909, 1210 (*Rev. of Neurol. and Psych.*, 1910, viii. 43).
105. Milligan, W., *Journ. of Laryngol.*, 1904; also *Trans. Otol. Soc. U. K.*, 1904, v. 25.
106. Minet and Lavoix, *L'Écho méd. du Nord*, 1909, 193 (abst. by J. D. Rolleston, *Rev. of Neurol. and Psych.*, 1909, vii. 479).
107. Miura, K., *The Philippine Journ. of Science*, 1907, ii. 409-412.
108. Molard, E., *La ponction lombaire dans le traitement du vertige labyrinthique*, Thèse de Paris, 1909 (abst. by Feindel, *Rev. neurol.*, Paris, 1909, xvii. 1305).
109. Moleen, *Journ. Amer. Med. Assoc.*, 1909, i. lii. 678, and *Rev. of Neurol. and Psych.*, 1909, vii. 4.
110. Mott, F. W., *Med.-Chir. Trans.*, Lond., lxxxiii. 209.
111. Nattier, Marcel, *Soc. méd. au IX<sup>e</sup> arrond.*, Paris, 1905.
112. Neumann, Heinrich, *Otitic Cerebellar Abscess*, Vienna (trans. by R. Lake, 1909).
113. Negro and Roasenda, *Reale accad. med. di Torino*, 7 giugno 1907.
114. Oppenheim, H., *Neurolog. Centralbl.*, Leipz., 1910, xxix. 114 (abst. by Edwin Bramwell, *Rev. of Neurol. and Psych.*, 1910, viii. 185); also 'Zur Lehre vom Kleinhirnbrückenwinkeltumor', *Neurol. Centralbl.*, Leipz., 1910, xxix. 338.
115. Orazio d'Allocco (*Rev. of Neurol. and Psych.*, *ibid.* 309), *La Riforma medica*, 1907, xxiii. 11 (*Rev. neur.*).
116. Ormerod, J. A., Article in *A System of Medicine* (Clifford Allbutt).
117. Parry, R. H., *Trans. Otol. Soc. U. K.*, 1904, v. 62.
118. Paton, L., *Brain*, Lond., 1909, xxxii. 65 (see also Jackson and Paton).
119. Pecori, G., *Il Policlinico*, 1906, xiii. 477-544.
120. Pezzi, C., *Gazzetta degli osped. e delle clin.*, 1907, xxviii. 567, and *Rev. neurol.*, Paris, 1907, xv. 1248.
121. Pritchard, *Trans. Otol. Soc. U. K.*, 1905, vi. ; also *ibid.*, 1902, ii. 132.
122. Panse, R., 'Schwindel,' *Zeitsch. für Ohrenheilkunde*, xli. 1902 (trans. *Arch. of Otol.*, 1902).
123. Pye-Smith, *Guy's Hosp. Rep.*, 1895, li. 223.
124. Pye-Smith (see Fagge and Pye-Smith).
125. Quincke, *Ponction lombaire*.
126. Raymond, F., *Progrès médical*, 1907, xxiii. 865.
127. Roasenda (see Negro and Roasenda).
128. Royet, de Lyon, *Soc. Franç. d'Otol., de Laryngol. et de Rhinol.*, 1906.
129. Russell, R., *Trans. Otol. Soc. U. K.*, 1905, vi. ; also *Lettsomian Lectures on Cerebellum*, Medical Society, London, 1910.
130. Sambon, *Journ. of Trop. Med.*, 1910.

131. Sergent and Grenet, *Bull. et Mém. de la Soc. méd. des hôp. de Paris*, 1908, 886-893.
132. Schupfer, F., *Clinica moderna*, 13 aprile 1907; and *Bollettino delle cliniche*, p. 289, luglio 1907.
133. Scott, S., *Proc. Roy. Soc. Med.*, 1908-9, Otol. Sect., ii. 4, 41; 1909-10, iii. 24.
134. Scott, S., *St. Bartholomew's Hospital Reports*, Lond., 1908, xlv. 113.
135. Scott, S., *Lancet*, Lond., 1910, i. 1601.
136. Scott, S., *Arch. of Otol.*, New York, 1908; also *Lancet*, Lond., 1910, i. 1601.
137. Scott, S., *Brit. Med. Journ.*, 1910, ii. 1675.
138. Scott and West (see West).
139. Sherrington, *Proc. Roy. Soc.*, 1896, 1897; also *Schäfer's Physiology*, ii. 1900.
140. Sneider (see Chavigny and Sneider).
141. Sorgo, *Monatschr. f. Ohrenheilk.*, 1901, 285 (quoted by Alagna).
142. Spiller, W. G., *Philad. Neurol. Soc.*, 1910.
143. von Stein, Stanislaus, *Appareil servant à déterminer les déviations des fonctions statiques du labyrinthe de l'oreille et sa démonstration*, Moscou, 1893.
144. Sternberg, *Zeitsch. f. Heilk.*, 1900 (quoted by Alagna).
145. Stewart, Purves, *The Diagnosis of Nervous Diseases*, Lond., 1908.
146. Stewart and Holmes, Gordon, 'Symptomatology of Cerebellar Tumours,' *Brain*, Lond., 1904, xxvii. 522.
147. Syme, W. S., *Brit. Med. Journ.*, 1909, i. 891.
148. Thomas, A., *Compt. rend. Soc. de Biol.*, 1896, 10<sup>e</sup> sér. iii. 299.
149. Thomson, St. C., *Proc. Roy. Soc. Med.*, Lond., 1908-9, ii. 2; *Laryngol. Sect.*, 16.
150. Toynbee, J., *Diseases of the Ear*, 1860 (Hinton's Edition, 1868, 55).
151. Turner, A., *Epilepsy*, Lond., 208.
152. Tweedie, *Brit. Med. Journ.*, 1907, ii. 713.
153. Urbantschitsch, E., *Monatschr. f. Ohrenheilk.*, xlv. 1; *Rev. of Neurol. and Psych.*, 1910, viii. 247.
154. Voltolini (cited by Alagna), *Virchow's Arch. f. Path. Anat. u. Physiol.*, 1861, xxii. 110.
155. Wagoner, *Med. Klinik*, 1909, xi.
156. Wallace, C., and Marriage, H. J., *Lancet*, Lond. 1904. i. 936, 1192.
157. Weber, Parkes, *Roy. Med.-Chir. Trans.*, 1900, lxxxiii. 185.
158. West, C. E., *Lancet*, Lond., 1904, i. 1570.
159. West and Scott, *Proc. Roy. Soc. Med.*, Lond., 1907-8, i. 3; Otol. Sect., 37.
160. West and Scott, *Proc. Roy. Soc. Med.*, Lond., 1908-9, ii. 3; Otol. Sect., 11.
- 160 a. Whalen, *The Laryngoscope*, 1906, No. 7.
161. Williamson, R. T., *Rev. of Neurol. and Psychiat.*, 1910, viii. 143.
162. Wilson, S. A. K., *Proc. Roy. Soc. Med.*, Lond., 1908-9, ii. 2; *Neurol. Sect.*, 52.
163. Wittmaack, *Zeitsch. für Ohrenheilk.*, lii. 1907 (abst. *Arch. of Otol.*, New York, 1907, xxxvi. 461).
164. Woolsey, *Amer. Journ. Med. Soc.*, Dec., 1903. Statistics on 101 cases of cerebral tumour (quoted by Thorburn, see *Med. Ann.*).
165. Yearsley, *Lancet*, Lond., 1908, ii. 871.





# INFECTION OF THE URINARY TRACT IN CHILDREN BY COLIFORM ORGANISMS

By W. M. JEFFREYS

With Plates 26 and 27

THIS is a condition which has recently attracted a good deal of attention and led to much discussion of its origin, course, and treatment. We are, however, still in ignorance of the actual mode of infection and of a sure means of curing the disease, and it is with the object of elucidating to some extent these problems that I have brought forward the present series of cases. They have been collected from the records of the Hospital for Sick Children, Great Ormond Street, and extend over the last nine years. They are sixty in number, and the ages of the patients range from four months to eleven years.

The diagnosis has been made by bacteriological examination of catheter specimens of urine, and only cases so diagnosed have been included in the series. The examinations were made by Dr. J. Graham Forbes, Pathologist to the Hospital. Sixteen of these cases came under my personal observation, and I was present at, or made, the post-mortem examination in six cases. The infecting organism was *Bacillus enteritidis* (Gaertner) in two instances, *Proteus vulgaris* in four, and in the remainder the *Bacillus coli communis*. I have included *Proteus*, because clinically these cases are indistinguishable from the others, and it is only by a bacteriological examination that their nature can be determined. The above organisms are the commonest infective agents of the urinary tract in children. Among 121 cases from the Hospital for Sick Children, 67 were due to coliform organisms, 37 to staphylococcus, 10 to streptococcus, 3 to pneumococcus, and 4 to other organisms. The reason for this preponderance of the coliform organisms is not quite clear, but *Bacillus coli communis* thrives in an acid medium, and is constantly present in the neighbourhood of the urinary organs. I will first give a table of the cases, followed by an analysis, then in detail some of the more important ones, and finally discuss the clinical features, etiology, pathology, and prognosis of the disease as shown by this series of cases.

Of the above cases there have been 14 this year (1910), of which five patients died of the disease and one of meningococcal meningitis, in which the coli infection was a complication. There were 16 cases in 1909, 12 cases in 1908, and 9 cases in 1907; the remaining 9 cases were scattered over the previous six years, and one of these died of the disease in 1905. This appears as though the disease were

No.	Age.	Sex.	Bowels.	Chief Symptoms.	Began as Pyelitis or Cystitis.	Evidence of Kidney Affection.	Severe or Mild.	Organism.	Result.
1	5 $\frac{1}{2}$	F.	Const.	Painful mictn.	Cyst.	Rt.	M.	B.C.C.	No improv <sup>t</sup>
2	8 $\frac{1}{2}$	F.		Turbid urine	Cyst.		M.	B.C.C.	No improv <sup>t</sup>
3	9	F.		Painful mictn.			M.	B.C.C.	No improv <sup>t</sup>
4	5 $\frac{1}{2}$	F.	Reg.	Haematuria and pain			M.	B.C.C.	Improved
5	1 $\frac{1}{2}$	M.	Diarrh.	Diarrh. & vom. pain		1 Rt. 2 Lt.	S.	B.C.C.	Death
6	10 $\frac{1}{2}$	F.	Const.	Frequency	Cyst.	Rt.	M.	B.C.C.	Improved
7	8 $\frac{1}{2}$	F.		Frequency pain		Rt.	M.	Proteus	Cured
8	1 $\frac{1}{2}$	F.		Muc. col.		Pus in urine	M.	B.C.C.	Improved
9	11	F.	Reg.	Pain abdomen		Rt.	M.	B.C.C.	Improved
10	10	F.	Const.	Pain abdomen	Pyel.	Rt. or Lt.	M.	B.C.C.	No improv <sup>t</sup>
11	7	F.	Diarrh.	Debility			M.	B.C.C.	No improv <sup>t</sup>
12	2 $\frac{1}{2}$	F.	Diarrh.	Haematuria	Pyel.	Rt.	M.	B.C.C.	Improved
13	3 $\frac{1}{2}$	F.		Painful mictn.			M.	B.C.C.	Cured
14	8 $\frac{1}{2}$	F.		Const.		Pain rt. side	Rt.	M.	B.C.C.
15	4	F.	Const.	Vom. pain abdomen			M.	B.C.C.	Cured
16	4	F.	Const.	Painful mictn.	Pyel.	Rt.	M.	B.C.C.	Cured
17	2	M.	Diarrh.	Frequency			M.	B.C.C.	Improved
18	1 $\frac{3}{4}$	F.	Muc. col.	Painful mictn.	Cyst.	Rt.	M.	B.C.C.	Improved
19	4 $\frac{1}{2}$	M.		Pyuria and pain	Pyel.	Rt. or Lt.	M.	B.C.C.	Cured
20	2 $\frac{1}{2}$	F.		Pain. defecn.	Pain abdomen	Pyel.	Lt.	M.	B.C.C.
21	7	F.	Diarrh.	Painful mictn.	Cyst.		M.	B.C.C.	Improved
22	6 $\frac{1}{2}$	F.	Muc. col.	Enuresis	Cyst.		M.	Proteus	Improved
23	8 $\frac{1}{2}$	F.		Frequency	Cyst.	Rt.	M.	B.C.C.	Cured
24	3 $\frac{1}{2}$	F.		Diarrh.	Foul urine		Rt.	M.	B.C.C.
25	8 $\frac{1}{2}$	F.	Reg.	Pain abdomen	Pyel.	1 Rt. 2 Lt.	M.	B.C.C.	Cured
26	5	F.	Reg.	Enuresis			M.	B.C.C.	Cured
27	8	F.	Diarrh.	Pain abdomen	Pyel.	1 Lt. 2 Rt.	M.	B.C.C.	Improved
28	3 $\frac{1}{2}$	F.	Reg.	Painful mictn.	Cyst.	Rt. or Lt.	M.	B.C.C.	Improved
29	6	F.		Frequency	Cyst.		M.	B.C.C.	Cured
30	8	F.		Frequency		Rt. or Lt.	M.	B.C.C.	Cured
31	2 $\frac{3}{4}$	F.		Painful mictn.	Cyst.		M.	B.C.C.	Cured
32	2 $\frac{1}{2}$	F.	Reg.	Painful mictn.	Cyst.		M.	B.C.C.	Cured
33	6	M.	Const.	Frequency		Lt.	M.	B.C.C.	Improved
34	1 $\frac{1}{2}$	F.	Const.	Vom., wasting	Cyst.		M.	B.C.C.	Improved
35	2 $\frac{3}{4}$	F.		Painful mictn.		Lt.	M.	B.C.C.	Improved
36	3 $\frac{1}{2}$	F.		Irreg.		Pain abdomen	Pyel.	Rt.	M.
37	3	F.	Reg.	Painful mictn.			M.	B.C.C.	Improved
38	1 $\frac{1}{2}$	F.	Diarrh. and vom.	Diarrh. & vom.			S.	Proteus	Cured
39	9	F.	Reg.	Pus in urine			M.	B.C.C.	Cured
40	5	F.		Painful mictn.	Cyst.		M.	B.C.C.	Cured
41	4	F.		Painful mictn.	Cyst.	Rt.	M.	B.C.C.	Cured
42	7	M.	Diarrh. and vom.				M.	B.C.C.	Death
43	8	F.	Ulcer. col.	Incontinence	Cyst.		M.	B.C.C.	Improved
44	11	F.					M.	B.C.C.	Death
45	7	F.		Appendicitis			M.	B.C.C.	Cured
46	1 $\frac{1}{2}$	F.	Diarrh. and vom.	Meningeal			M.	B.C.C.	Improved
47	6	F.	Diarrh.	Painful mictn.	Cyst.	Rt. or Lt.	S.	B.C.C.	Death
48	5 $\frac{1}{2}$	F.	Diarrh.	Painful mictn.	Cyst.	1 Rt. 2 Lt.	S.	B.C.C.	Improved
49	1 $\frac{1}{2}$	F.	Const.	Meningeal		1 Rt. 2 Lt.	S.	Gaertner	Improved
50	1 $\frac{1}{2}$	M.		Meningeal		Rt. or Lt.	S.	B.C.C.	Death
51	10 $\frac{1}{2}$	F.		Const.	Pain abdomen	Pyel.	1 Lt. 2 Rt.	S.	B.C.C.
52	7 $\frac{1}{2}$	F.	Reg.	Meningeal			S.	B.C.C.	Death
53	1 $\frac{1}{2}$	F.	Diarrh.	Pain. retention	Cyst.		M.	Proteus	No improv <sup>t</sup>
54	1 $\frac{1}{2}$	M.		Diarrh. & vom.		Rt. or Lt.	S.	B.C.C.	Death
55	8	F.		Diarrh.	Incontinence	Cyst.		M.	B.C.C.
56	1 $\frac{1}{2}$	F.	Const. and diarrh.	Wasting		Rt. or Lt.	S.	B.C.C.	Death
57	2	F.	Reg.	Convulsions	Cyst.		M.	B.C.C.	Improved
58	8	F.		Foul urine			M.	Gaertner	Improved
59	4 $\frac{3}{4}$	F.		Diarrh.		Wasting		M.	B.C.C.
60	6 $\frac{1}{2}$	F.	Const.	Precipitancy		1 Rt. 2 Lt.	M.	B.C.C.	

becoming more common and increasing in severity; there is no doubt, however, that cases were frequently overlooked, and in the fatal cases no bacteriological examination made, for on examining the older case-books and post-mortem records of the Hospital, I find a fair number of cases presenting similar clinical features and similar pathological changes post mortem to those of the present series. The fact that all the fatal cases except one occurred in 1910, however, would suggest that the disease is of peculiar virulence at the present time. There is no particular age incidence, neither is there any evidence that it is more common at one time of the year than another. The sexual incidence agrees with that generally noted; there were 53 females and 7 males.

Only 10 dated the trouble from some previous illness, generally an acute specific fever. The condition of the bowels is worthy of note. In 34 cases there was definite evidence of bowel trouble of one kind or another, in 10 cases the bowels were noted as regular, and in 16 there was no evidence pointing to bowel trouble.

With regard to the chief symptoms complained of, in 37 cases they pointed to bladder trouble, usually painful micturition; 3 cases were brought up for diarrhoea and vomiting, 9 for abdominal pain, 5 with meningeal symptoms, 4 for debility, and in 2 there were no symptoms. Four cases were discovered in children suffering from some other illness. Twenty-one began with symptoms pointing to bladder trouble and 9 with symptoms suggesting pyelitis. In 30 cases there was no evidence to suggest the mode of onset. There was evidence pointing to pyelitis in 30 cases; in 12 the right kidney only was affected, in 3 the left only. The renal trouble began in or was confined to the right kidney in 17 cases, the left in 5; in one of the latter the right kidney was more markedly affected than the left. In 8 cases there was no evidence to show which kidney was first affected. Examination of the urine shows that pus was present in nearly every instance, 56 out of 60. Albumin was present in 45 and blood in 15. The urine was acid in 39 cases, alkaline in 7, neutral in 1, and in the remaining 13 cases no note was made of the reaction. Casts were noted as being present four times.

Only 21 were discharged as cured, that is to say with no symptoms and no pus in the urine. Nine died; of these, 6 died of the urinary trouble and 3 of some other disease, of which the urinary infection was a complication. Six were discharged 'in statu quo ante' and 23 as 'improved'; this usually meant that symptoms had abated but that pus was still present in the urine.

### Cases.

*Case LIV.* C. M., male, 4 months: admitted May 30, 1910. There was a history of diarrhoea and vomiting for nine days. On admission he was collapsed and cyanosed, with contracted pupils; he appeared to be in a meningeal state and lumbar puncture was performed, with negative results; the urine was then found to contain pus and *Bacillus coli*. He died on the twelfth day of his illness. *Post-mortem*: the kidneys showed a mottled appearance, the capsules



stripped easily, the pelves and ureters were not dilated but contained creamy pus, and the bladder was not hypertrophied.

This is the only really acute case of the series, and presumably there had not been time for the secondary changes in the bladder, ureters, and pelves to become established. Another point of interest is that there were patches of hyperaemia at the hepatic and splenic flexures of the colon. The brain and other organs were healthy.

*Case XXXVIII.* K. B., female, 1 year and 2 months: admitted Sept. 9, 1909. This and the four following cases are instances of the mild form of the disease. There was a history of diarrhoea and vomiting for six weeks, and she was collapsed on admission, with normal temperature. She remained drowsy and vomited occasionally, and the diarrhoea persisted for a while and then improved. On October 14 she became worse and the temperature rose; she became jaundiced, the stools were clay-coloured and the temperature remained irregular. The infective agent was *Proteus vulgaris* and a vaccine of this organism was given, with rapid improvement. The temperature became normal and remained so till November 17, when it again rose (Fig. 1); a second injection of vaccine was given and the temperature fell; the child made a good recovery and left the hospital cured on December 31. This case illustrates the good effects of vaccines in some instances.

*Case LX.* E. C., female, 6½ years: admitted Sept. 17, 1910. She gave a history of precipitancy of micturition since March, with feverishness and shivering attacks off and on. There were intermittent attacks of fever with pain and tenderness, first in the right loin and then in both, but always more marked in the right; the right kidney could be felt in these attacks, which only lasted about three days at first, and were always associated with marked constipation; later the fever became irregular and she was treated with vaccines (Fig. 2, p. 270).

This patient is still under observation, but serves to show the relation between bowel trouble and the condition of the kidneys and urine.

*Case XLV.* M. V., female, 7 years: admitted December 13, 1909. The history pointed to recurring 'bilious attacks', and recently frequent and painful micturition; she was also said to have had appendicitis. She was subjected to cystoscopic examination on three occasions, and treated with injections of iodoform emulsion. Very little improvement followed, so on January 27 the appendix was removed. The child was later sent to a convalescent home and returned cured. This case suggested cyclic vomiting, and was also interesting as being cured by appendicectomy, the appendix containing a scar as evidence of recent inflammation.

*Case XXIII.* A. P., female, 8 years and 1 month: admitted Feb. 3, 1908. She had frequency of micturition with pain for four years, getting worse recently; she had also wasted considerably. The urine contained pus and *Bacillus coli*; the frequency of micturition and pain were very severe. The bladder was examined with the cystoscope and nothing very definite seen; the bladder only holding an ounce of fluid. She was treated with bladder irrigation and injections of iodoform emulsion, with considerable improvement, but the frequency and pain continued. On March 24 another cystoscopic examination was made and the bladder found to be much more tolerant, but there was a considerable amount of mucus obscuring the field. The frequency continued and she complained of pain in the right iliac fossa. The child was wasting and greatly distressed with the urinary trouble, so on July 7 the appendix was removed; it was found to be very long and its tip adherent to the lower pole of the right kidney; the caecum was noted also to have a long mesentery. The child improved from this

date and eventually made a complete recovery. This is another case of cure following removal of the appendix. She was seen again on November 3, 1910, and the urine was found to be sterile.

*Case IX.* B. A., female, 11 years: admitted Dec. 29, 1906. There was a history of pain in the hypogastrium fortnightly for ten years. This time there had been pain for three weeks, with foul urine, frequency, and pain on micturition. Cystoscopic examination showed hyperaemia of the trigone, with blood oozing from the right ureter. On January 21 the right kidney was explored and incised; nothing abnormal was detected and the wound was drained. She made a fair recovery, but still had pus in the urine on discharge from hospital on February 14. She was readmitted on October 9, giving the same history as before, suggesting cyclic vomiting. There were no signs of organic disease except that the urine still contained pus and *Bacillus coli*. She was treated with urotropin and discharged at the end of October 'improved'.

This case illustrates the chronicity of a great many of them, and shows that the actual damage to the kidney may be very small as judged by the naked eye. It is also suggestive of the association of cases of cyclic vomiting with this condition as pointed out by Thursfield (14).

*Case XLIX.* C. L., female, 6 months: admitted March 25, 1910. This and the succeeding cases are instances of the more severe form of the disease. For a week she had had meningeal symptoms. On admission the case was taken for one of meningitis; this was partly on account of the fact that the child had congenital amaurosis, which was only discovered later. Lumbar puncture was performed, but the cerebro-spinal fluid was found to be normal; the urine was then examined and found to contain pus and *Bacillus enteritidis* of Gaertner. The right kidney became enlarged and tender, followed by the left; the right subsided somewhat, but the left increased; the child appeared to be dying, but the left kidney was explored and opened, a large quantity of purulent fluid escaping. She made a good recovery and left the hospital with a fistula in the left loin, which closed up finally on October 16, but the urine still contains pus.

This case illustrates the meningeal appearance of some of these babies, which was in this instance enhanced by the amaurosis. It also illustrates the chronicity of the disease.

*Case XXVII.* E. T., female, 8 years: admitted April 23, 1908. She was feverish, with pain in the left side of the abdomen and wasting, worse the last few days, bowels loose. The child was very ill, with temperature rising to 105°; the pain and tenderness on the left side subsided and she improved, but had a relapse with symptoms of a similar kind on the right side. An operation was performed and the right kidney removed; it was large, with numerous pale areas beneath the capsule. Section showed numerous inflammatory foci with necrotic centres, also a few haemorrhages. She made a slow recovery and left the hospital on July 5, but the urine still contained pus cells.

This points to an affection of both kidneys, the one removed showing very extensive damage, yet the child made a comparatively good recovery.

*Case V.* H. K., male, 4 months: admitted July 20, 1905. Had had diarrhoea twelve days, vomiting ten days, pain in abdomen nine days, and had been feverish and short of breath four days. He was in a meningeal state on admission, with irregular fever. A mass resembling a large kidney was felt in the right loin, but no other signs. The following day the meningeal symptoms had subsided; the urine was scanty, acid, and contained many pus cells. On July 28 he collapsed and was restored with difficulty. A pathological report on the urine by Dr. Forbes showed the presence of pus and *Bacillus coli* in pure growth. He was treated with potassium citrate and sodium bicarbonate until

the urine became alkaline. The child remained drowsy, with irregular fever; meningeal symptoms appeared from time to time and he occasionally had diarrhoea. On August 25 he was circumcised and collapsed under the anaesthetic; he was revived, and lived till Sept. 4, when he died. *Post-mortem*: the circumcision wound was sloughy, the liver was pale and fatty and the spleen congested and friable. The kidneys were large, equal, lobulated, and pale; on section the definition of the tissue was blurred. The pelves were not dilated or thickened. The ureters were not distended. The bladder was normal. Other organs were normal. A microscopic section of the kidneys showed cloudy swelling of the cells of the cortical tubules, and many of these tubules contained debris and hyaline casts; there were also a few small haemorrhages and cell infiltration of the interstitial tissues, as well as congestion of the cortex and the glomeruli, with some cell exudation between the glomerular tufts and Bowman's capsule.

In this case circumcision seems to have accelerated the end, and is suggestive that cases reported to have occurred after circumcision may in reality have been cases of the mild type in which the symptoms were aggravated by the operation (9). The post-mortem findings in this case were characteristic of acute sepsis rather than of coli infection, and were perhaps connected with the sloughy state of the wound.

*Case LVI.* R. F., female, 1 year and 1 month: admitted July 5, 1910. There was a history of wasting for three weeks. On admission she had signs of pneumonia at the right apex; this subsided and pus was discovered in the urine; she was treated with alkalis, antiseptics, and irrigation of the bladder, without avail, and after a prolonged illness she died on Sept. 28. *Post-mortem*: the kidneys showed the characteristic mottling on the surface with numerous pale infarcts; on section the pelves and ureters were dilated and contained purulent fluid; the bladder was only slightly hypertrophied. There was recent pneumonia at the right apex and the other organs were healthy (Plate 27, Fig. 7).

*Case L.* L. L., male, 5 months: admitted April 11, 1910. Very constipated for a month, with some vomiting and much wasting. He was circumcised four days before admission and died the day after admission. *Post-mortem*: the kidneys, ureters, and bladder resembled those in Cases 47 and 50; namely, multiple necrotic infarcts in both kidneys, which were enlarged, dilated pelves and ureters, and some hypertrophy of the bladder wall. This shows the danger of circumcision in these cases; the condition obviously had existed long before the operation.

*Case XLVII.* F. P., female, 6 years: admitted Dec. 30, 1909. There was a history of straining at micturition for six weeks, with pain in the bladder. She was a wasted child and had frequency of micturition. She was treated in various ways, alkalis, antiseptics, &c., but with no improvement. She became uraemic, with amaurosis and eventually coma, and died on March 12. *Post-mortem*: both kidneys were large, the right more than the left, the capsules stripped easily and the surfaces were irregularly mottled; on section these pale mottlings were seen to be the bases of small necrotic infarcts. The pelves were dilated and contained purulent fluid. The ureters were both markedly dilated and tortuous, with several kinks, but there was no evidence of obstruction. The bladder was greatly hypertrophied and its mucous membrane deeply congested. This case is characteristic of the chronic fatal ones.

*Case LI.* J. C., female, 10 years and 3 months: admitted April 18, 1910. She gave a history of headache, vomiting, and pain in the stomach for a year; worse the previous three days. On admission she was thin, pale, and slightly jaundiced, nothing abnormal was found in the urine; next day she had pain and tenderness in the left side of the abdomen and the urine contained a little albumin. On



April 21 there were a few casts and pus cells in the urine, and from this time onwards the urine was never free from pus. On April 26 the jaundice had gone and there was pain and tenderness in the right loin. On April 29 she developed frequency of micturition, and on May 10 tenderness and pain in the left loin. On May 12 she was drowsy, and was thought to be uraemic, as No. 47 had been. She was given vaccines and gradually improved, and left hospital on July 18 for a convalescent home, apparently quite well except for a little pus in the urine. On August 8 she returned and reported herself at the hospital; she appeared to be in perfect health, but there was still a little pus in the urine; she had vomited that morning, but looked so well that this was attributed to a slight attack of indigestion. On her way home from hospital she became hemiplegic on the left side, had several fits, and died next morning. *Post-mortem*: there was a large haemorrhage in the right occipital lobe of the cerebrum, with a smaller one on the left side; a small haemorrhage was also seen in the pons. Both lungs showed numerous haemorrhagic infarcts. The small intestine showed numerous small submucous haemorrhages throughout its whole length. The right kidney was atrophic and adherent to the perirenal tissues, the capsule was firmly adherent at both poles, but free in the middle; on section the upper and lower poles were fibrous and shrunken and the central part comparatively healthy, except for small infarcted areas similar to those in Cases 47 and 50. The left kidney was hypertrophied, had several old infarcts, and on section showed a good deal of interstitial infiltration. Both ureters were small and straight and the bladder was very slightly hypertrophied. The heart and other organs were healthy (Plate 26, and 27, Fig. 6).

This case shows the danger these patients run as long as they have pus in the urine. It is not quite easy to interpret the changes found post mortem, but presumably multiple emboli had lodged in the lungs, brain, and intestine; no thrombus could be found in the renal veins, however. The normal appearance of the ureters and bladder was probably associated with the slight symptoms noticeable with regard to frequency of micturition, which only lasted a day or two.

### *Diagnosis and Clinical Features.*

The diagnosis, of course, rests with the bacteriological examination of the urine, but even here there may be fallacies; an organism may be grown from a catheter specimen where there has been no suspicion of any urinary trouble. I examined catheter specimens from forty cases, taken haphazard in the wards, with a view to finding cases with bacilluria, but without symptoms; five of these grew *Bacillus coli* on the first examination, but a second proved sterile; in none of these cases was pus present in the urine. The explanation is that it is extremely difficult to be sure of an aseptic specimen in a child, especially a female, so that unless there are symptoms pointing to urinary trouble and pus is present a second examination should always be made. There are other well-known fallacies, such as pus or blood from the vagina in a standing specimen being mistaken for pus or blood from the urinary tract. A common history is that the child's urine is offensive; there are other causes for offensive urine, however; the urine of some children tends to become very offensive on standing, although quite sweet when passed. The urine may become turbid with bacteria in an hour or two, although there is no infection of the bladder. Fallacies of

another kind are met with, as when the bacilli are mistaken for acid fast organisms, as pointed out by Dudgeon (5).

The character of the urine is well known in these cases; it is pale, unusually opalescent, and contains a deposit of mucus and pus in variable quantity; one day the urine may be almost clear and the next there may be a dense deposit of muco-pus an inch deep in the urine glass; this may vary in each specimen passed during twenty-four hours and is frequently very dense after one of the characteristic bouts of fever and pain; this suggests that there is temporary retention in some part of the tract, which is quite in accordance with the extremely tortuous ureters seen in many of the cases post mortem. Obvious blood is not common, but there are usually red corpuscles to be seen under the microscope, and sometimes patients are brought to hospital because of blood in the water. A trace of albumin is nearly always present, but a dense cloud is rare; this again is in accordance with the post-mortem findings, as a diffuse parenchymatous nephritis is not as a rule found. The reaction is nearly always acid; the alkaline instances may be due to a mixed infection either within or outside the body. Casts are not often found, but are probably often overlooked.

With regard to the clinical features of these cases, there is great variation, and unless there are symptoms pointing to urinary trouble their nature is very likely to be overlooked altogether. Classification should be based upon the mode of infection, but as it is usually impossible to say how any given case was infected this is impracticable. They have been divided into acute and chronic cases, but as most of them have an acute onset and become chronic, this is obviously unsatisfactory. There was only one really acute case in the present series, namely Case 54, which ran its course in twelve days.

I have found it most convenient to classify in three groups:—I, in the first year of life; II, mild cases; III, severe cases. In the first group, which may be mild or severe, the clinical features are completely different from those seen in older children; babies cannot say where their pain is, and the crying is often mistaken for mere naughtiness; again, who can say if a baby has frequency of micturition? There were 7 cases of this series occurring in the first year of life; 1 was apparently produced by catheter, 3 were brought up for diarrhoea and vomiting and 3 with meningeal symptoms. Three of these cases ran a mild course, 3 were fatal, and 1 patient was operated on for pyonephrosis. This looks as if it were a more serious condition in the first year of life, but it must be remembered that it is so likely to be overlooked at this age that only the severe cases are noticed. Another peculiarity of those in the first year of life is that the preponderance of the female sex is much less marked. Out of the 7, 3 were males and 4 females, and out of the 7 males of the whole series 3 were under one year of age. In John Thomson's (13) series of 25 cases in the first two years of life there were 4 males, all in the first year; the female preponderance was shown even here, however; namely, 21 females to 4 males; this, however, is not nearly so marked as the proportion in older children. The explanation is not obvious, but there is less difference between the sexes at this age. In the second, or mild,

group, of which there were 49 in the series, there is generally a history of trouble with micturition of one kind or another, often of long duration; the children are generally wasted, pale, or with an 'earthy' tint of the skin; if there is incontinence, they frequently have a distinctive odour, easily recognized if once experienced. The urine in these cases does not always have an offensive odour, but when present it has a peculiar fishy character, as described by Pardoe (10). These patients are liable to periodic attacks of fever, accompanied by pain and tenderness; these usually subside in one or two days, but if they be severe or prolonged there is pain, tenderness, and enlargement of the second kidney as well. These attacks are often associated with constipation, and if this is relieved the attack usually ends, only to recur later. The urine frequently contains excess of pus after one of these attacks, as mentioned above. They run a chronic course as a rule, but may clear up very rapidly on apparently very simple treatment, or none at all; they usually resist all forms of treatment, however. In the third, or severe, group, of which there were 9 in the present series, the onset is variable; it may be with micturition trouble, or with pain in one or both loins; in babies either with diarrhoea or meningismus; the disease may run a short course, ending fatally, as in Case 54, or more usually a chronic course; the child wastes to an extreme degree and dies of uraemia. Case 51 was of an unusual character, and death from cerebral haemorrhage must be an extremely rare event.

### *Etiology.*

The causation of this condition has been a much debated problem, and so far no satisfactory conclusions have been arrived at. Three possible channels of infection are usually described, namely:—(1) by the urethra to the bladder, and thence to the kidneys, via the ureters, (2) by the blood stream, (3) by the lymphatics from the bowel. I think it probable that there are instances of all three modes of infection, but there is very little evidence that the disease begins as a septicaemia and secondarily involves the kidneys. The two commonest modes must be either by an ascending infection from the urethra, or by a direct infection from the large intestine by way of the lymphatics. The great argument in favour of an ascending infection is the large preponderance of the female sex, the short, wide female urethra being more likely to be infected than the male urethra. It is often pointed out that female babies get the vulva infected from soiled napkins, but every baby has an infected vulva from this cause, and in the first year of life the female preponderance is less marked than in later life.

Another point in favour of an ascending infection is the large number of cases which apparently began as a bladder infection as compared with those that began apparently as a renal infection; I say apparently, but there are cases with no local symptoms, and it is possible that the part to which symptoms are first referred is not the part in which the disease commenced. In the present series there were 21 apparently beginning in the bladder to 9 apparently beginning in

the kidneys. I think there is no doubt that ascending infection does take place in some cases. Bond (2) has shown that particles of pigment may ascend mucous tracts in an opposite direction to the stream of contents.

*Bacillus coli* is present in the urethral orifices of both sexes. Melchior (8) found that *Bacillus coli* was present in the urinary meatus of 50 per cent. of males; this, however, would lead one to expect the disease far more commonly in males. Barnard (1) suggests that any abnormality in the periodic flushing of the urinary passages favours an infection, and I have collected 27 cases of enuresis, dating from birth, in older children, of whom 19 were girls and 8 boys, showing that this is more than twice as common in girls as in boys. In my series of cases, however, there were only 4 in which enuresis had dated from birth.

It may be that, after all, the sexual incidence has nothing to do with the mode of infection, for, as Garrod pointed out at the discussion on this subject at the meeting of the British Medical Association in July, 1910, there are certain diseases confined almost entirely to one sex, such as pyloric hypertrophy in male infants and sulphonal poisoning in women, in which the incidence at present is entirely without explanation. I think that the evidence goes to show that the condition starts as an ascending infection in a certain number of cases, but that this number is usually overestimated.

I will now bring evidence to show that the third method of infection is a very important and, perhaps, the commonest one of the three. The association of bowel trouble is a very common one; out of the 60 cases there was evidence of bowel trouble in 34; they were noted as regular in only 10, and it is reasonable to suppose that constipation may have been present in a certain number of the remainder, seeing how commonly this is overlooked by parents, and not noted in hospital records. In John Thomson's 8 cases (12), published in 1902, 7 were markedly constipated; and out of his 25 cases published in 1910, 12 suffered from habitual constipation (13). Kerley (7) also draws attention to intestinal troubles associated with this condition. This bowel trouble is used as an argument in favour of each of the three possible paths of infection, but here another factor comes in, namely, that the right kidney is affected far more often than the left.

In my cases in which one kidney only was affected, it was 12 times on the right side and only 3 times on the left. Further, the kidney trouble was confined to, or began in, the right in 17 cases, and in the left in 5, and in one of the latter the right kidney bore the brunt of the attack (Case 51). Barnard (1) records 6 cases in adults, all on the right side; Rolleston (11) notes that it is commoner on the right than the left side, as does Box (3); and here let me observe that there may be another reason for the affection of the right kidney in pregnancy than the pressure of the uterus on the right ureter (6). It seems to me there must be some close association between bowel trouble and the affection of the right kidney.

Now, if the disease starts as a septicaemia, why does it not affect both

kidneys equally, and other organs as well? and if it be an ascending infection, why does it chiefly affect the right side? There is a close anatomical association between the right kidney and the ascending colon, caecum, and appendix. In chronic obstruction of the rectum stercoral ulceration is found at the opposite end of the large bowel, namely, in the caecum and ascending colon, and it is reasonable to suppose that this part is also damaged to some extent in constipation. In this connexion it is interesting to consider the two cases cured by removal of the appendix, for which I am indebted to Mr. Waugh, who had another similar case, the notes of which I am unable to obtain. Moreover, in Case 44, in which the child died of general lymphatic tuberculosis, there were tuberculous ulcers in the caecum. In most of the fatal cases there was nothing very definite observed in the intestines, but they had all run a chronic course, and perhaps the original lesion had healed; in Case 54, however, where the child died in the acute stage at the end of 12 days, there were hyperaemic patches in the hepatic and splenic flexures, and in this case both kidneys were equally affected and the bladder was normal.

It seems difficult to explain the female preponderance on this hypothesis, unless we are to suppose female children more frequently constipated than male, as is the case in adults. In babies, moreover, where there is less distinction between the sexes, the female preponderance is less marked. I suggest, therefore, that a large number of the cases are due to direct transference of organisms from the large intestine to the right kidney.

### *Pathology.*

I will describe the pathological changes found in Case 54, as an instance of an acute fatal case, and then the changes found in the mild cases, and finally those in the severe chronic cases.

*Case LIV.* The body of a well-nourished baby; this is in contrast to the marked emaciation usually found in the chronic fatal cases. The kidneys were not enlarged, the capsules stripped easily, and the surfaces showed a few pale areas, similar to those found in the chronic cases. On section the pelves were not dilated, but contained thick, white, purulent fluid. The substance of the kidneys showed pale tracts running through it, similar to those on the surface, with swelling and irregularity of the tubules. The ureters were not dilated or tortuous; on opening them, both were found to contain pus, similar to that in the pelves; the mucous membrane was swollen and congested in the upper parts, but normal in the lower. The bladder wall was not thickened, the mucous membrane showed no swelling or congestion, and the orifices of the ureters appeared normal. In this case the hepatic and splenic flexures of the colon were congested, the liver was pale but firm, and the other organs healthy. Examination of the pus from the ureters showed *Bacillus coli communis*.

This is the earliest case on which a post-mortem examination was made. It appears that lesions of the large intestine had allowed transference of the organisms to the kidneys, giving rise to the pale necrotic areas and the congestion of the upper part of the urinary tract, but in spite of the passage of pus

over the lower parts of the ureters and bladder they had remained healthy up to the time of death.

The only evidence which I have of the conditions prevailing in the mild cases comes from cystoscopic examinations, and two post-mortems on cases in which death was due to other causes. Cases 42 and 44 both died of other diseases, one from amyloid disease, following a chronic sinus, the other from general lymphatic tuberculosis.

The first showed no changes in the kidneys other than those of marked amyloid disease, and the ureters and bladder were normal. There had been no symptoms during life that could be attributed to *Bacillus coli* infection. The second case showed tuberculous ulcers in the caecum, but no obvious abnormality of kidneys, ureters, or bladder. In this case also there had been no urinary symptoms during life. The inference is that it is only in the severe cases that marked changes in the kidneys occur, and that changes in the bladder do not occur unless there is also pain and frequency of micturition.

Eleven of the mild cases were examined with the cystoscope. In Case 10 the patient had slight frequency, but no pain with micturition; the bladder appeared normal. In Case 12 the patient had haematuria, but no frequency of or pain on micturition. Cystoscopic examination showed a normal bladder with blood oozing from the right ureter. In Case 13 the patient had no symptoms referable to the bladder and cystoscopic examination revealed nothing abnormal. In Case 14 the same conditions prevailed. In Case 24 the patient had no symptoms. Cystoscopic examination showed slight redness of the lips of the right ureter and of the base of the bladder. In Case 25 the patient had frequency and slight pain on micturition. Cystoscopic examination showed redness of both ureters and much mucus on the bladder wall. In Case 28 the patient had pain before and after micturition; there was a plug of mucus in both ureters and the bladder was congested. In Case 31 the patient had painful micturition. Nothing abnormal was detected by cystoscopic examination. In Case 48 the patient had pain and frequency. Cystoscopic examination showed that both ureters were congested, but the bladder normal. In Case 53 the patient had painful micturition, but nothing abnormal was detected by cystoscopic examination. In Case 55 the patient had frequency, incontinence, and blood in the urine. Cystoscopic examination showed an ulcer at the apex of the bladder. These results indicate that pain and frequency may be present with very slight bladder change. Redness of one or both ureteral orifices seems to be the commonest pathological change found, in these cases, by means of the cystoscope.

In the severe chronic cases there were a number of characteristic changes found post mortem; the liver usually showed slight fatty change; the other organs, except the urinary, were healthy. The kidneys were usually slightly enlarged and showed a mottled appearance on the surface, the dark areas being congested and the light areas the bases of small degenerating infarcts, the centres being necrotic and the periphery infiltrated with polymorphonuclear leucocytes, destroying the neighbouring tubules. The capsules stripped easily, and on section the

kidney substance presented a number of radiating pale streaks, the bases of those that reached the surface forming the pale areas mentioned above. The pelves were usually dilated and contained purulent fluid, the lining membrane being congested. The bladder, in some cases, showed great thickening with small cavity and congested mucous membrane (Cases 47 and 50). In Case 27 the kidney removed by operation showed a more acute stage, in which the pale areas were going on to abscess formation. In Case 51 there were depressed areas in the kidneys, like old infarcts with adherent capsule, suggesting healing of some of these areas; there were also a few recent ones, indicating that the process was still active. This case showed many exceptional features, and I have described it more fully elsewhere.

### *Prognosis.*

This condition is sometimes looked upon as one of the more trivial of children's complaints, but the above table shows that it is one of the most stubborn diseases to cure, and has a considerable mortality, especially of late. In this series there were six deaths due to the infection, and four of these were in babies, a mortality of 10 per cent. Even cases that escape with life may drag on for many months, and cannot be said to be free from danger till pus has been absent from the urine for at least several days. Nobody could have appeared in more robust health than the patient in Case 51 on the morning she reported herself at the hospital, but she was dead within twenty hours. Of the remainder, only twenty-one were discharged cured. The symptoms usually respond readily to any form of treatment, but it seems almost impossible to rid them of pus in the urine, and so long as this is present, they are liable to relapse or even sudden death.

### *Treatment.*

It is difficult to draw conclusions from the treatment of the above cases, as most of them had more than one form of treatment. One case recovered spontaneously, and Batty Shaw (4) reports another. Altogether 14 cases were untreated, except by rest in bed and nursing; of these, 1 was cured, 5 went out unchanged, 2 were 'improved', and 6 died, 3 of the latter from some other complaint. Forty-six cases were treated with drugs, or local applications to the bladder, and 20 of them were cured, 4 with washing out the bladder, 1 with alkalis by the mouth, 5 with antiseptics by the mouth, and 1 with vaccines. The remainder had various combinations of the above methods.

The usual treatment was upon three lines: 1. Alkalis. 2. Urinary antiseptics. 3. Local treatment to the bladder. These were usually combined, and I cannot say that any of them seemed of very much value. The alkalis have been very widely used, with the idea that *Bacillus coli* does not thrive in an alkaline medium; this is not strictly true; it grows quite well in an alkaline medium, but also grows well in an acid medium, while the usual pyogenic

organisms will not. The reason why the urine of these cases is acid is because *Bacillus coli* does not split up urea. I have not found the alkalis of any great value, neither have I found the urinary antiseptics of much use. Local treatment by washing out the bladder and injecting iodoform emulsion seems to have a beneficial result; possibly the iodoform finds its way to the pelves of the kidneys in the way that pigment particles do, as shown by Bond (2). In the severe cases vaccines appear to improve the general condition of the patient, but seldom remove the pus from the urine.

I think it most important to treat the bowel condition by washing out the large intestine and keeping it acting by means of aperients, but being careful not to produce further irritation of the large intestine, as is very likely with aperients. Judging by the three cases cured by appendicectomy, it seems well worth while resorting to this measure in stubborn cases.

In conclusion, there are one or two points to which I should like to refer. Thursfield has suggested a relation between this condition and cyclic vomiting; two of the present series presented symptoms similar to cyclic vomiting, and in cases of the latter the urine should always be examined for pus (14). The disease occasionally presents a similarity to appendicitis, especially in the acute exacerbations with pain in the right side, constipation, and fever, and in such cases a search for pus in the urine should be made, but even if it is found, the complaint may still be appendicitis, or both, and it is very likely that removal of the appendix will cure one or both diseases.

I wish, lastly, to express my indebtedness to Dr. Garrod, Dr. Voelcker, Dr. Colman, Dr. Batten, Dr. Thursfield, Mr. Arbuthnot Lane, Mr. Kelloch, Mr. Stansfield Collier, Mr. Corner, Mr. Waugh and Mr. Fairbank, of the Hospital for Sick Children, Great Ormond Street, for permission to make use of cases under their care, and to Mr. G. B. Wainwright for the photographs.

### *Conclusions.*

The disease is usually due to transference of organisms directly from the large intestine to the right kidney owing to some damage to the former as by constipation. Ascending infection takes place in a minority of cases and primary blood infection is rare.

Treatment is difficult, but it is most important to attack the bowel condition, combining this with vaccines and local applications in certain cases. If there is evidence of past or recent appendicitis the appendix should be removed.

The disease must not be looked upon as a trivial complaint; it usually runs a chronic course, and not uncommonly ends fatally.



## REFERENCES.

1. Barnard, *Lancet*, Lond., 1905, ii. 1243.
2. Bond, *Brit. Med. Journ.*, 1905, ii. 232.
3. Box, *Lancet*, Lond., 1908, i. 77.
4. Batty Shaw, *Clin. Journ.*, Lond., 1908, xxxi. 273.
5. Dudgeon, *Lancet*, Lond., 1908, i. 616.
6. Hicks, *Brit. Med. Journ.*, 1909, i. 203.
7. Kerley, *Arch. Pediat.*, 1909, xxvi. 217.
8. Melchior, quoted by B. Shaw (see 4).
9. Morse, *Amer. Journ. Med. Sci.*, 1909, N. S., cxxxviii. 313.
10. Pardoe, *Brit. Med. Journ.*, 1910, ii. 1129.
11. Rolleston, *Practitioner*, Lond., 1910, lxxxiv. 439.
12. Thomson, J., *Scot. Med. Surg. Journ.*, 1902, xi. 7.
13. Thomson, J., *Quart. Journ. Med.*, Oxford, 1909-10, iii. 251.
14. Thursfield, *Hospital*, Lond., 1909, xlv. 453.

## DESCRIPTION OF FIGURES.

PLATE 26, FIG. 3. Case LI. Piece of jejunum, showing numerous submucous haemorrhages.

FIG. 4. Case LI. Longitudinal section of cerebellum, medulla, and pons, showing haemorrhage in the latter.

FIG. 5. Case LI. Horizontal section through cerebral hemispheres, showing a large haemorrhage in the right occipital lobe and a smaller one in the left.

PLATE 27, FIG. 6. Case LI. Kidneys, ureters, and bladder, showing atrophic right kidney laid open, hypertrophied left kidney, normal ureters and bladder.

FIG. 7. Case LVI. Showing mottled surface of right kidney, from which the capsule has been stripped. The left kidney has been divided longitudinally and shows the pale infarcts and the dilated pelvis. The ureters are dilated and the bladder practically normal.



FIG. 3.



FIG. 4





# THE THIRD SOUND AND *B* WAVE IN SLOW HEART ACTION; SOME POSSIBLE FALLACIES IN THE INTERPRETATION OF RECORDS

By J. DAVENPORT WINDLE

THE occurrence of a third heart sound between the normal second and succeeding first sound has long been recognized as present in certain cases. Several observers have directed attention to its occasional occurrence in healthy people with slowly acting hearts. A true third sound is distinguished from a reduplication of the second sound in that it always occurs at a longer interval than the second element of a reduplicated second sound; and it is generally heard only in the neighbourhood of the apex; if heard elsewhere its greatest intensity is at, or near, the impulse. A. G. Gibson (1) and Hirschfelder (2) independently observed an additional wave in the jugular pulse tracings in some instances in which a true third heart sound was present in normal individuals.

This wave is indifferently named the *b* wave of Gibson or *h* wave of Hirschfelder. This wave occupies a position in the early diastolic phase of the venous curve, occurring almost invariably within  $\frac{2}{3}$  sec. of the negative phase *v-y* in the normal curve. The time relation to the succeeding *a* wave varies with the rate of the pulse. Its cause is ascribed to the inrush of blood into the ventricle, floating up the cusps of the tricuspid valve and bringing about a transient apposition, which it is thought may be sudden and vigorous enough, when the venous pressure is high, to give rise to a sound. Whether this is the true explanation is not certainly known, nevertheless the intimate association of a third sound and the *b* wave has been so definitely established as to render it probable. On the other hand, however, the *b* wave frequently occurs independently of a third sound, and in some instances in which the sound is heard a corresponding wave is not invariably present in the venous tracing (Fig. 20).

Thayer (3) states that a third sound can be heard in the neighbourhood of the impulse in about 30 per cent. of normal individuals, lying on the left side, with a frequency greatest in the first and second decades, amounting to 58.9 per cent. and 84.4 per cent. respectively. From my own observations in this connexion, a third sound in healthy individuals is of rare occurrence.

Repeated examination of ninety-three healthy boys, aged 10-18 years, inmates of a training institution, brought to light only one case in which a third sound

was present; it was, however, so feeble and inconstant that it is doubtful if it would be detected in ordinary routine examination. The venous tracing in this case shows a well-marked extra wave (Fig. 1).

On the other hand, a decided *b* wave was present in the venous tracings obtained from six of these boys, in none of whom was there any suspicion of a third sound. Sinus irregularity was present in all these instances, and the pulse was slow, from 50 to 60 per minute. A notable feature was the presence of the *b* wave only during the long pulse pauses. Fig. 2 is an illustrative record from this group.

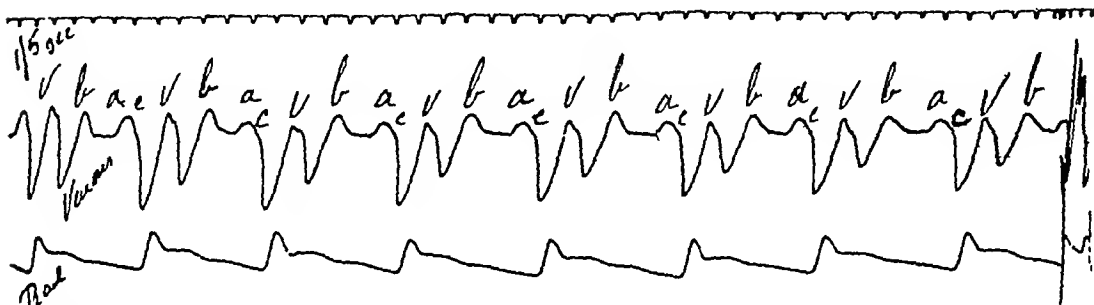


FIG. 1. From a healthy boy, aged 13½ years. Pulse rate 53 per minute; slight sinus irregularity is present; an additional wave—*b*—occurs in the diastolic portion of the venous curve.



FIG. 2. Jugular and radial tracing from a healthy boy, aged 14, taken two minutes after exercise. Marked sinus irregularity is present, slowing coincides with expiration, the *b* wave shows only in the slowest pulse periods.

In another series of observations on a hundred healthy young people with pulse rates from 50 to 70, six cases were met with in which a pronounced *b* wave was present in the venous tracing; in one instance only was there a clearly marked third heart sound. The jugular and radial tracing from this case is reproduced in Fig. 3.

The case from which this tracing was obtained was a healthy youth, six feet in height, and of very spare build; he was in good health and had never had any illness of moment. There was no evidence of organic disease in any of the systems of the body. The pulse rate was 48 per minute; slight sinus irregularity was present; the wave was slow in onset and well sustained. The systolic blood pressure was 130–135 mm. The chest was long and narrow. The heart's impulse was visible in the fifth space four inches from the middle line; it

corresponded in rhythm with the radial pulse. There was no precordial thrill. The first and second sounds were clear, well struck, and normally spaced. The second sound was followed by one of lower pitch and intensity, but of almost equal duration. It occurred at an interval approximately equal to that between the first and second sounds. The triple rhythm may be phonetically represented by Lūb-dūp-tā. The third sound, although faint, was clear and had none of the characters of a murmur; it occurred later than the second beat of a reduplicated second sound would have been expected, and it was heard only in the neighbourhood of the impulse. The sound was audible both standing and lying, but it was best marked in the left lateral position during transient suspension of breathing. So far as could be estimated by auscultation, the time of the

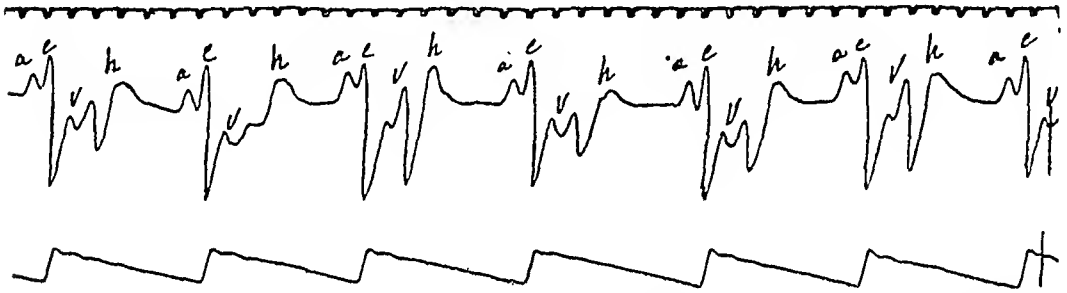


FIG. 3. Record of jugular and radial pulse from a healthy youth, aged 18. The pulse rate is 48 per minute, slight sinus irregularity is present, the jugular curve shows a well-marked early diastolic wave (*h*).

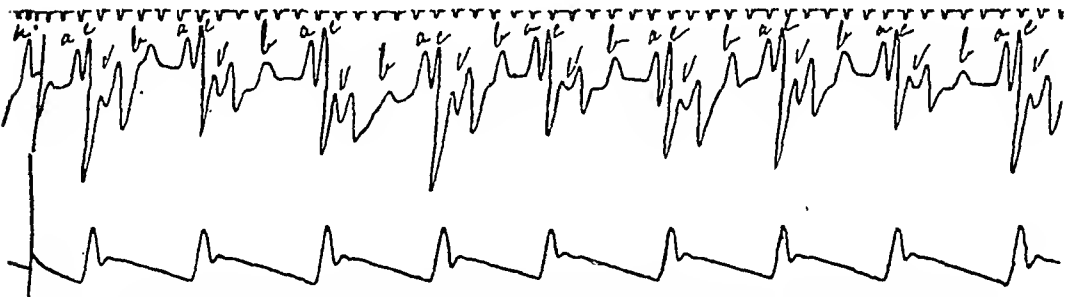


FIG. 4. Obtained from same case as Fig. 3, a year later. The *b* wave occupies a position later in diastole; pulse rate 50.

sound coincided with the extra wave in the venous tracing. Fig. 4 was obtained from the same case a year after Fig. 3.

In this figure it will be found on measurement that the *b* wave occurs slightly later in diastole than in Fig. 3. If the rate of the heart were increased by any means the third sound could not be heard when a certain degree of quickening was reached; and this was coincident with the disappearance of the extra wave from the venous tracing. This is illustrated in Figs. 5, 6, and 7, from records taken at the same time as Fig. 4, after the inhalation of three minims of amyl nitrite.

Immediately after commencing inhalation (Fig. 5) the pulse rate quickened to 60 per minute; with this rate the *b* wave is still present. The last two beats

in this tracing are at the rate of 75; coincidentally the *b* wave disappears, and continues absent with the increase of pulse rate up to 100 per minute (Fig. 6). A period of five seconds elapsed between Figs. 6 and 7; as the pulse slows, marked irregularity occurs (Fig. 7); with the slower beats the wave is again in

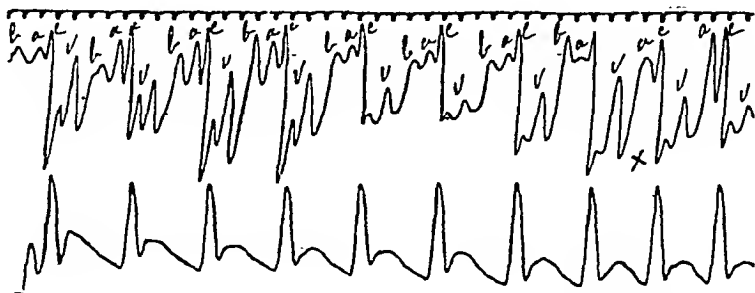


FIG. 5. Taken at the same time as Fig. 4, after three minims of amyl nitrite, with a pulse rate of 60. *a*, *c*, *v*, and *b* waves are present; the *b* wave is absent in the last two beats, which are at the rate of 75 per minute.



FIG. 6. Nitrite of amyl; stage of throbbing, pulse rate 100, *b* wave absent.

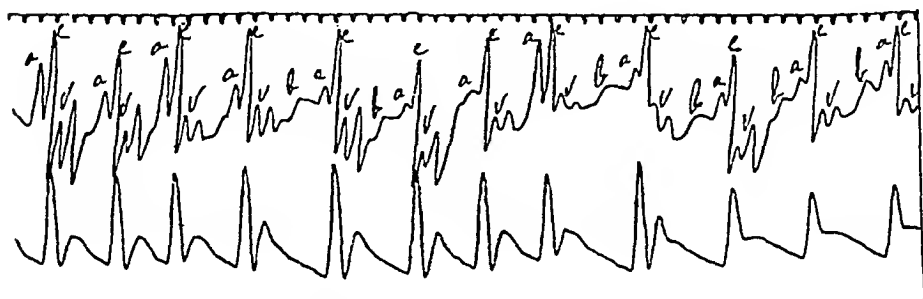


FIG. 7. Taken 5 seconds after Fig. 6. Sinus irregularity present; the *b* wave shows only in the longer pulse periods.

evidence (compare Fig. 2); with a rate of 60 and below it persisted and the tracing again has the feature shown in Fig. 4.

The absence of the third sound and the disappearance of the *b* wave from the venous curve are explicable on current views as to the mechanism of diastolic closure of the auriculo-ventricular valves. It is claimed by Henderson (5), whose views are accepted by Hirschfelder (6), that this results from the elastic recoil of the heart walls, following upon rapid and complete distension of the

ventricle, the degree of which is dependent upon the venous pressure and the rate of the heart. If the rate of the heart is quick, filling of the ventricle is interrupted by the next systole, and as a result its distension is incomplete. When the heart's action is slow, filling of the ventricle lasts longer, and reaches full distension; at this moment closure of the auriculo-ventricular valves occurs, thence blood accumulates in the veins, at first rapidly and later in diastole more slowly. The angle made by these two portions of the venous curve forms the *b* wave. Robinson (4) and Thayer coincidentally found a wavelet (Fig. 8) on the cardiogram in cases in which the *b* wave and third sound were present, which is ascribed to filling of the ventricle. It corresponds to the crest of the *b* wave in the venous tracing.

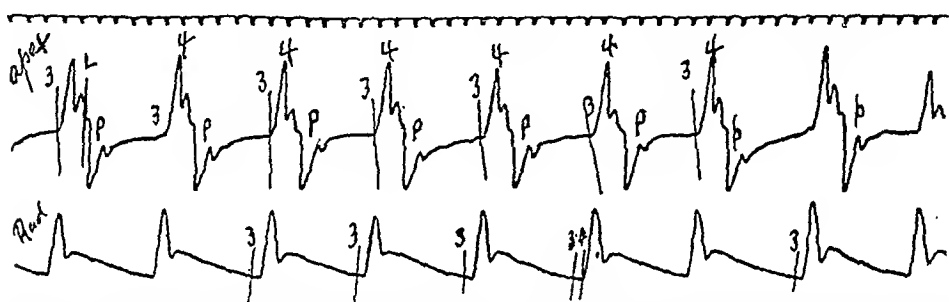


FIG. 8. Apex and radial tracing from the same case as Fig. 4. The curve of ventricular filling is interrupted by the wave *p*, ascribed to recoil of the ventricle at the end of diastolic inflow.

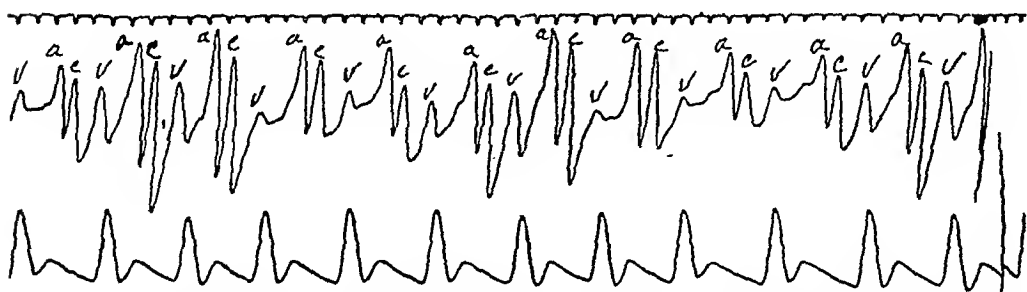


FIG. 9. From a case of compensated mitral regurgitation. Pulse rate 70; the jugular curve shows the usual *a*, *c*, and *v* waves. A few doses of digitalis had been given when this record was taken.

These considerations lead to the inference that an extra venous wave due to the factors mentioned may first appear coincidentally with the slowing of a quickly acting heart below a certain rate. This not unfrequently happens during the slow pulse periods in sinus irregularity, and I have met with a number of instances in which the *b* wave was first evident in the venous curves after full slowing of the heart under drugs of the digitalis group. Records of illustrative examples are reproduced in the following figures.

Fig. 9 is from a patient, aged 20, with compensated mitral regurgitation of rheumatic origin. He complained of breathlessness on exertion and precordial pain. Digitalis had been given for a few days before this record was taken.



The usual pulse rate was 80-85. On many occasions I have taken records from him and found only the normal *a*, *c*, *v* waves present. Under ten minims of tincture of digitalis thrice daily for a fortnight the pulse rate fell to 50; a pronounced *b* wave is present in the jugular tracing (Fig. 10). With the quickening of the pulse after leaving off the digitalis the *b* wave was no longer evident. Another instance is illustrated in Figs. 11 and 12.

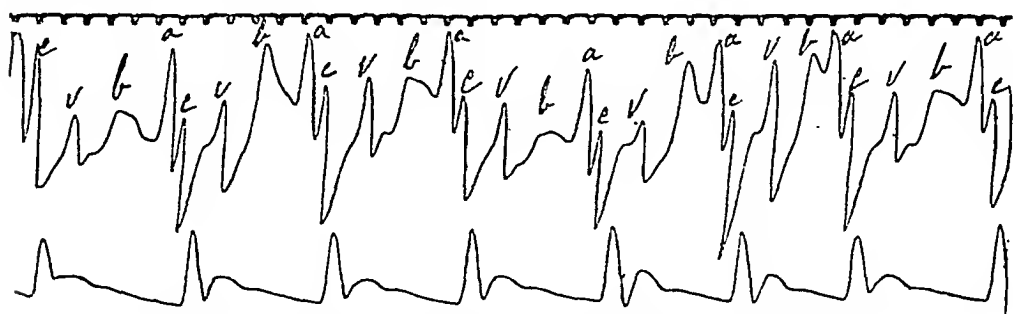


FIG. 10. From the same case as Fig. 9, after digitalis. Pulse rate 50; there is a well-marked *b* wave in the jugular tracing.

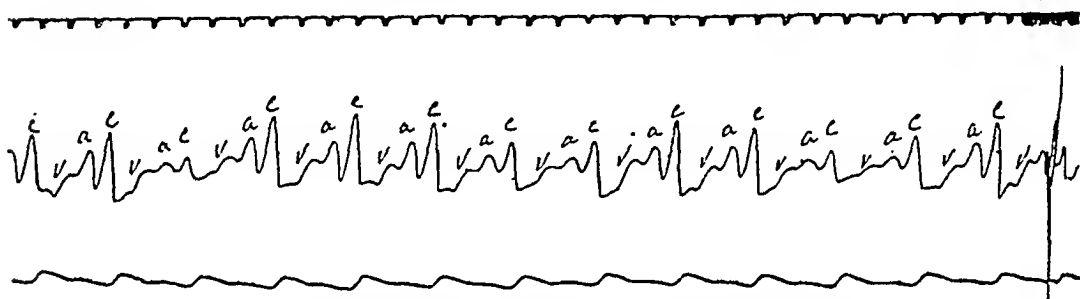


FIG. 11. Record from a case of mitral regurgitation. Pulse rate 100 per min.; the venous curve shows the usual *a*, *c*, *v* curves. Before digitalis.

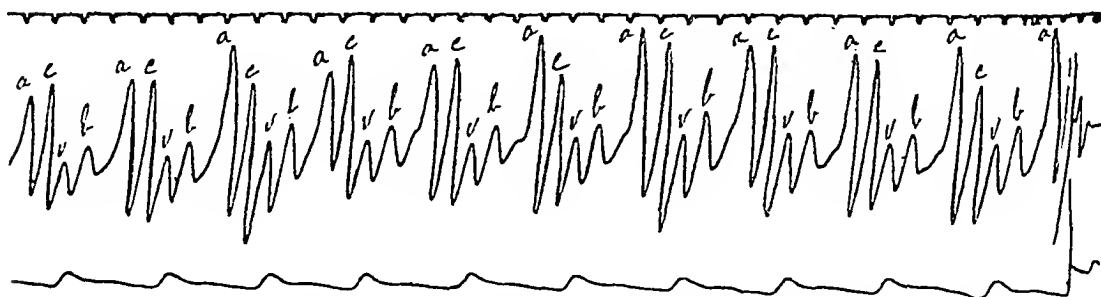


FIG. 12. From the same case as Fig. 11, after digitalis. Pulse rate 75; an early diastolic wave *b* shows in the venous tracing.

These records were obtained from a man, aged 28 years, complaining of shortness of breath. There was no enlargement of the heart, but a long, soft, mitral systolic murmur was present. Fig. 11 is the record taken when the case first came under observation. The pulse was regular, 100 per minute; the venous curve shows the usual *a*, *c*, *v* waves. Fifteen minims of tincture of digitalis were taken thrice daily for a week. The effect on the pulse is shown in Fig. 12; the

rate fell to 75 and a marked *b* wave is present. A further degree of slowing under the continued use of digitalis in this case is shown in Fig. 18, in which it will be seen that the *b* wave occupies a position later in diastole, and a marked sinus irregularity due to digitalis is present. The records shown in Figs. 13 and 14 were obtained from a healthy youth aged 17, with a perfectly normal heart with a slight sinus irregularity (Fig. 13). Digitalis was given with the object of raising the blood pressure, which was abnormally low. The effect on the pulse was to slow the rate, and increase to a marked degree the irregularity (Fig. 14).

It will be seen in the tracing before digitalis that there is no evidence of a *b* wave; the slowest beats in this record are at the rate of 72 per minute. After digitalis (Fig. 14) the *b* wave is well marked with the slowest radial

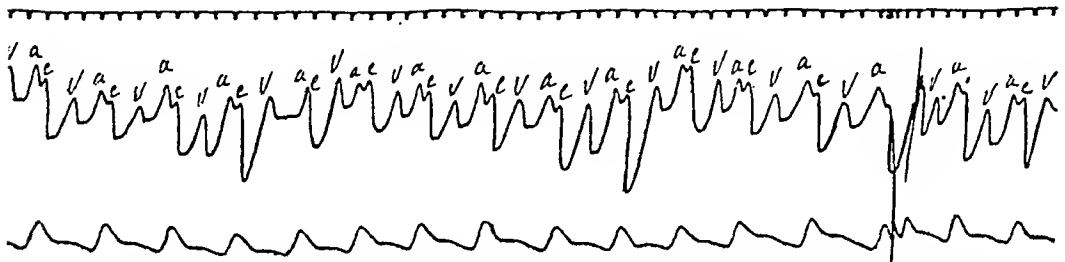


FIG. 13. From a case of sinus irregularity in a healthy youth, aged 17; the rate of the slowest beats is 72 per min. Venous record shows *a*, *c*, and *v* waves.

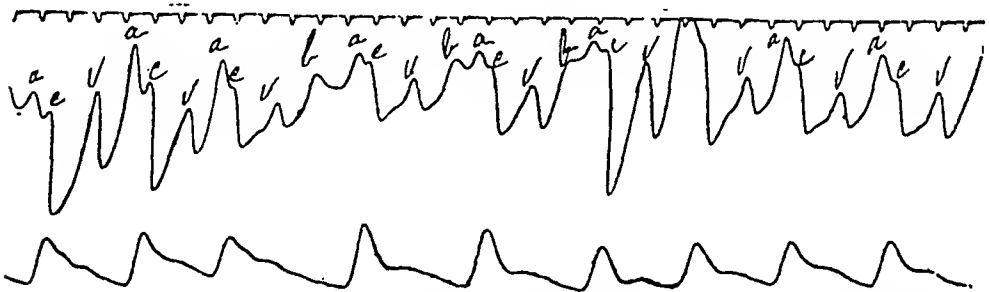


FIG. 14. From the same case as Fig. 13, after digitalis. The irregularity is more pronounced; the slowest pulses are at the rate of 60-65. The corresponding venous curve shows a marked *b* wave, which is absent in the quicker beats.

beats, which are at the rate of 60-65. With the quicker beats the *b* wave is absent.

Fig. 15 was obtained from a case of partial heart-block resulting from the administration of tincture of squill. An extra wave *b*<sup>1</sup> appears in the jugular tracing following the blocked auricular waves, which I suggest bears the same explanation as the *b* wave. In this case a loud, clear, third sound was audible at the impulse during the long pauses; whether associated with the *a* or *b*<sup>1</sup> wave could not be certainly determined.

Fig. 16 is an instance of associated *b* wave and third sound first noticed on slowing of the heart in the course of Bright's disease. The patient, a youth aged 14½ years, came to me in June, 1910, for a certificate of health, to comply



resulting from pathological conditions, and at times the associated clinical circumstances may easily lead to error in interpretation.

In cases of slight sinus arrhythmia in healthy young people, the irregularity is sometimes greatly increased shortly after exertion. A remarkable degree of aperiodic slowing may occur, corresponding to which, at times, an extra wave is evident in the venous curve. The presence of this wave, together with the long radial pulse pauses, may closely simulate extra-systoles (Fig. 2).

In cases in which the *b* wave constantly recurs in an apparently mid-position between the preceding and following *a* waves, the tracing may bear a close likeness to one of heart-block. This is well shown in Fig. 4. In this case the abnormally slow pulse, together with the presence of an extra wave seemingly falling at a regular interval between the preceding and following *a* waves, might readily suggest a 2:1 heart-block—the third sound being attributed to independent auricular contractions. When the additional wave first appears on slowing of the heart under digitalis, the circumstances strongly

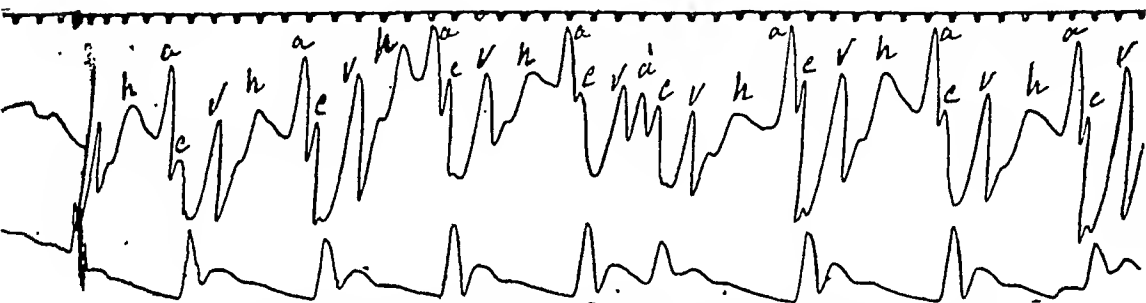


FIG. 17. To illustrate the constant time relationship of the *h* wave to the preceding systolic period which is maintained with change of rhythm.

suggest heart-block. The distinction is readily made on measuring the time relationships of the extra wave. It will be found that while the *b* wave bears a constant relationship to the *preceding* *a* or *c* waves, which is maintained, with variations in the rate of the pulse, its position in relation to the succeeding systolic period is only constant so long as the pulse is regular; if the rate quickens or slows, the *b* wave approaches or recedes from the succeeding *a* or *c* waves (compare Figs. 5-7).

These features are further illustrated in Fig. 17. The auricular extra-systole occurs at the time the *b* wave is due; the extra-systolic beat is succeeded by the *b* wave at the regular interval. Sinus irregularity is present, the position of the *b* wave in relation to the succeeding *a* or *c* waves increases and decreases with the rate of the pulse, whilst its time relation to the preceding systolic period keeps constant. In heart-block the extra wave (*a*) falls at a constant time interval in relation to both the preceding and succeeding systolic period, which remains the same with variations in the rhythm of the pulse.

*Apparent lengthening of the a-c interval.*

Quickening of the pulse takes place at the expense of the period in which the *b* wave occurs—the interval in the venous curve between the fall *v-y* and the succeeding *a* wave.

When the pulse rate approaches 100, this period is too short for the *a* and *b* waves to be differentiated (Figs. 6 and 7). With a rate of about 70-80 the two waves often merge into each other, so that a single long wave results, which may be fallaciously interpreted as due to impairment of conductivity.

Thus, in Fig. 18, in which sinus irregularity is present, the *b* and *a* waves are clearly differentiated in the slowest beats, and the *a-c* interval is  $\frac{7}{5}$  of

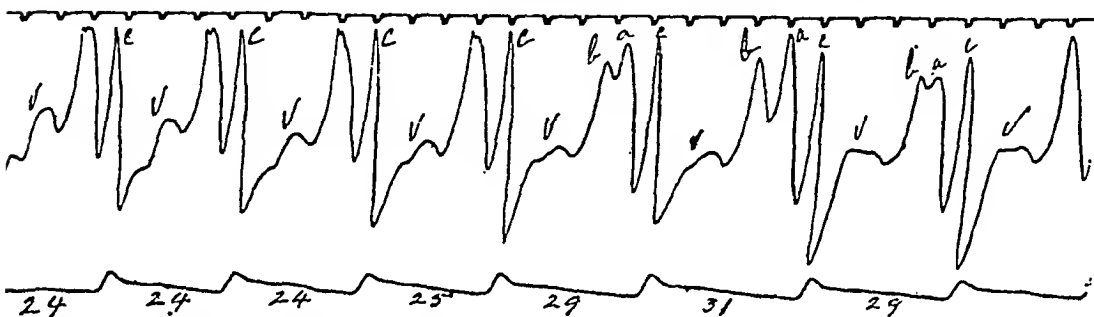


FIG. 18. From the same case as Fig. 11. Sinus irregularity is present, due to digitalis. With the quicker beats the *b* and *a* waves coalesce, causing an apparent increased *a-c* interval. The *b* and *a* waves are differentiated in the slowest beats; the *a-c* interval is slightly under  $\frac{1}{2}$  sec. The pulse periods are converted into terms of  $\frac{1}{10}$  inch linear.

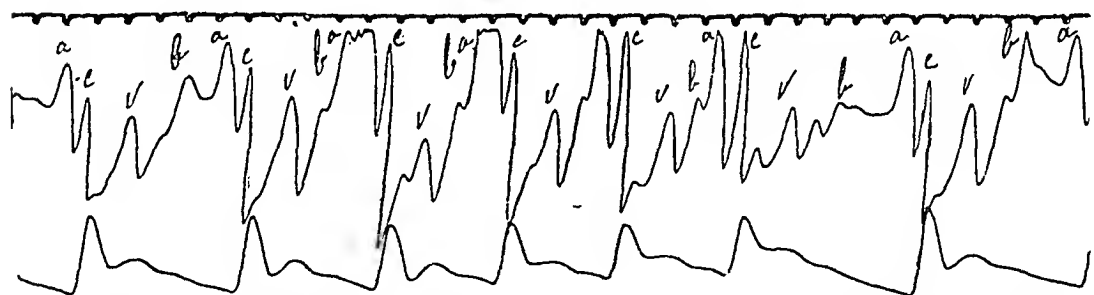


FIG. 19. Shows the same as Fig. 16. The irregularity occurred on swallowing. With the initial quickening of the pulse there is an apparent increase in the *a-c* interval which is brought about by the blending of the *a* and *b* waves.

a second. The first four beats in the tracing are the quickest; the apparent increased *a-c* interval corresponding to these beats is brought about by the coalescence of the *a* and *b* waves.

It will be evident, too, that these waves are most clearly differentiated in the sixth beat, which is the slowest. On the succeeding quickening of the pulse with the next beat the waves again coalesce. The same relationships are evident in Fig. 19 from another case.

The irregularity occurred on swallowing. The coalescence of the *b* and *a* waves causing an apparently increased *a-c* interval during the quick period is well shown. The value at times of this fact in diagnosis is illustrated by the

following case recently under my care. The patient, a female aged 54 years, presented marked arterial degeneration with high blood pressure and enlarged heart. A clearly struck and well-spaced third sound was present.

The pulse was 60 per minute; the venous tracing shows no extra wave (Fig. 20). The *a-c* interval in many of the beats is  $\frac{2}{3}$  sec. These circumstances

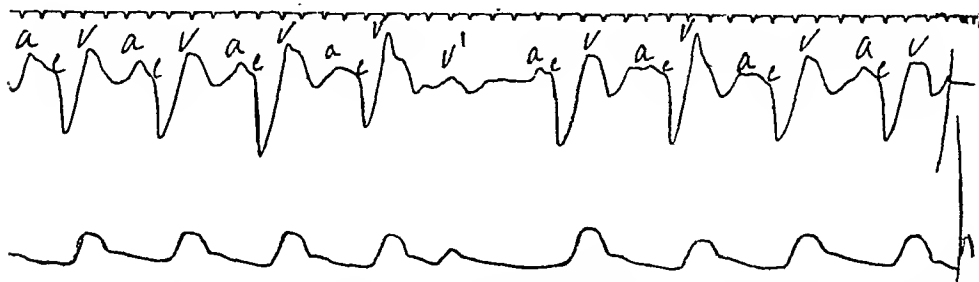


FIG. 20. From a case of arterio-cardio-sclerosis with well-marked third heart sound. There is no extra wave in the venous curve, in which the *a-c* interval in some of the beats is  $\frac{2}{3}$  sec. After the long pause succeeding the ventricular extra-systole the *a-c* interval is decreased.



FIG. 21. From the same case as Fig. 20, after 180 minims tinct. digitalis. Pulse slowed to 50. A *b* wave now shows in the tracing. The *a-c* interval is  $\frac{1}{3}$  sec.

suggested impairment of conductivity. After taking three drachms of the tincture of digitalis the record shown in Fig. 21 was obtained.

The pulse slowed to 50, and the venous tracing shows an apparent increase in the *a-c* interval to  $\frac{3}{4}$  sec., or thereabout. On careful scrutiny, however, it is evident that two waves occupy the interval *v-y* to *c*, and the *a-c* time interval is normal, the apparent increase in the previous record being due to the blending of these waves.

### Summary.

1. A third heart sound with an associated *b* wave was present in two out of 193 observations on normal individuals. The pulse rate was abnormally slow and sinus irregularity present in both cases.

2. In 13 instances of the number of persons examined, a decided *b* wave was present in the venous tracing, in none of which was a third sound heard. Marked sinus irregularity was present in 9 of the records. The pulse rate in these cases varied from 50 to 60 per minute.

3. When the pulse rate was quickened in cases in which the *b* wave was persistently present under normal conditions it did not show in the tracing when the pulse rate exceeded 80 per minute. When associated with sinus arrhythmia it was absent from the venous curve when the arrhythmic beats approached this rate.

4. The *b* wave may first appear in the venous tracing coincidently with regular slowing of the heart to a rate of from 50 to 70 per minute under digitalis. This may be brought about in the normal heart (Fig. 14). In no case observed was there a third sound present.

In slowing resulting from partial heart-block due to squill an extra wave succeeding blocked auricular waves is shown to occur. Coincidently with the establishment of heart-block in this case, a clearly marked third sound was present.

5. Venous curves showing the *b* wave may present a close resemblance at times to those resulting from extra-systoles or cases of heart-block.

6. With a certain rate of pulse the *b* and *a* waves may fall together and give an appearance to the curve closely simulating an increased *a-c* interval.

#### REFERENCES

1. Gibson, A. G., *Lancet*, Lond., 1907, ii. 1380.
2. Hirschfelder, A. D., *Johns Hopkins Hosp. Bull.*, Balt., 1907, xviii. 265.
3. Thayer, W. S., *Bost. Med. and Surg. Journ.*, 1908, clviii. 713.
4. Robinson, G. C., *Amer. Journ. Med. Sci.*, Philad., 1908, N. S., cxxxv. 670.
5. Henderson, Y., *Amer. Journ. Physiol.*, Bost., 1906, xvi. 325.
6. Hirschfelder, A. D., *Diseases of the Heart and Aorta*, Philad. and Lond., 1910.

## PAROXYSMAL TACHYCARDIA OF VERY BRIEF DURATION

By E. E. LASLETT

SINCE the introduction of the graphic method a more exact analysis of the nature of paroxysmal tachycardia may be made, and it is now proved that there are several types of this affection which differ from one another in the site of origin of the stimulus production. Cases of the auricular type have been published by Schmoll, Hirschfelder, Hay, Cowan McDonald and Binning, and Lewis. The case here recorded presents the peculiarity of frequent short attacks, and thus affords the valuable opportunity of studying the mode of onset and termination of the paroxysms. It appears to be similar in many respects to a case of Mackenzie's, of which an exhaustive study has recently been published by Lewis. I am indebted to the papers of the last-named author for much help and guidance in the interpretation of the pulse curves obtained from my own case.

The patient was a woman aged 72 years, who had been under my care since June last. Considering her age she enjoyed a fair measure of health and was able to do her own housework in comparative comfort. She was extremely deaf, and although she was intelligent there had been great difficulty in obtaining a history. The fact that she was subject to attacks of paroxysmal tachycardia was discovered accidentally during the investigation into the nature of the markedly irregular pulse which she always had. On inquiry it was found that for some months at least, perhaps for a year or two, she had been troubled with attacks of 'fluttering' in the chest, which came on particularly when she was tired. She did not seem to have paid much attention to them, and her friends had not been able to give me much information, but so far as can be made out they consisted of a series of short paroxysms spread over one or two hours rather than of one continuous attack. Apparently she had long periods of freedom from paroxysms (they had been almost absent for three months), and when liable to them they might come on at any time of the day, but perhaps particularly when she was tired. Flatulence also seemed to be an exciting cause, and with relief of this the attacks often ceased. The tachycardia very rapidly disappeared when the patient lay down, and it practically never occurred when she was in bed at night. On this account and because she was a private patient seen at home there was great difficulty in obtaining simultaneous jugular and radial curves during a paroxysm. She appeared to be always conscious of even



the shortest attacks of four beats only. As usual the paroxysms were accompanied by peculiar symptoms referred to the chest, which the patient found it difficult to describe. They consisted of 'fluttering' at the heart, a sense of oppression in the lower part of the chest which seemed to rise up into the neck, and after a short period some degree of dyspnoea and restlessness. If at all prolonged she had to sit down. The patient showed the usual senile changes. The pulse was of moderate tension, 60-70 per minute and irregular. The nature of the irregularity will be considered later. The heart sounds were normal. No apex beat could be felt. As regards the remaining organs of the body there was nothing special to be noted.

*The nature of the paroxysm.* I have observed hitherto only short attacks, the longest being not much more than half a minute in duration, and the longest attack of which a curve has been obtained consisted of only eleven beats (Fig. 1). From a study of the simultaneous jugular and radial curves there can be no doubt that it is a question of paroxysms of the auricular type, that is to say, that the site of the stimulus production lies somewhere in the auricle. Further than this it is not possible to proceed in the localization, in the absence of electro-cardiograms. Lewis's work has shown that the evidence of electro-cardiograms taken in conjunction with that of the venous curve permits of a considerable advance towards a more exact localization of the stimulus formation. Under favourable conditions, however, bearing in mind the evidence thus obtained, the venous pulse alone when carefully analysed may afford reliable proof of the exact origin of the paroxysm. Thus Lewis has published a case of paroxysmal tachycardia in which, from the evidence of the electrical variations, the origin of the stimulus was located in the lower levels of the auricle in the neighbourhood of the node of Tawara. In this case, as clearly shown in the venous curve, the  $a-c$  interval during the paroxysm was much shortened (0.06 sec.). In the present case it is sufficient to point out that the  $a-c$  interval during the paroxysms is the same length as in the slow period (namely about 0.16 sec.), and therefore the site of the stimulus is probably well away from the lower level of the auricle.

*Pulse curves.* The radial curve of a typical paroxysm is shown in Fig. 1. It consists of eleven beats commencing after what is possibly a normal pulse period, and ends in a pause. There appears to be a rise of pressure during the paroxysm as shown by the slight rise of the pulse curve. Simultaneous jugular and radial curves are shown in Figs. 2 and 3. The venous curves are often defective. Although there was in this patient a fairly well-marked jugular pulse, owing to the wasting of the neck tissues and the varying rigidity of the sternomastoid muscle it was very difficult to get a good continuous venous curve. The paroxysm may start after a pause as in Fig. 1, or it may start immediately after a normal beat as in Fig. 3. The paroxysm terminates usually in a long pause, but occasionally, as in the first paroxysm in Fig. 3, by a series of auricular extra-systoles. It will be seen that as represented in the radial curve they are weaker beats than those of the paroxysm, the pressure

tending to fall. Here they take the place of the usual pause and are followed immediately by an apparently normal beat. These auricular extra-systoles have been carefully studied by Lewis. In his case they frequently introduced a paroxysm and less frequently interrupted the terminal pause. Lewis lays stress on their different appearance in the radial curve as a means of differentiating them from the beats of the paroxysm proper, and in confirmation of this he finds that they give an electro-cardiogram which is different from that of the latter.

*The pulse between the paroxysms.* The pulse is hardly ever regular between the paroxysms, but for the most part is of rhythmical, bigeminal, or

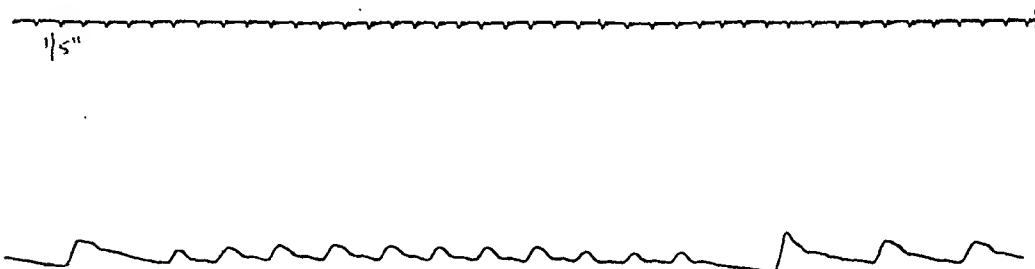


FIG. 1. A paroxysm of eleven beats which begins and ends with a pause of the same length. There is a slight rise in the curve indicating a rise in pressure. The first normal pulse period is prolonged. Pulse rate during the paroxysm 142 per min.

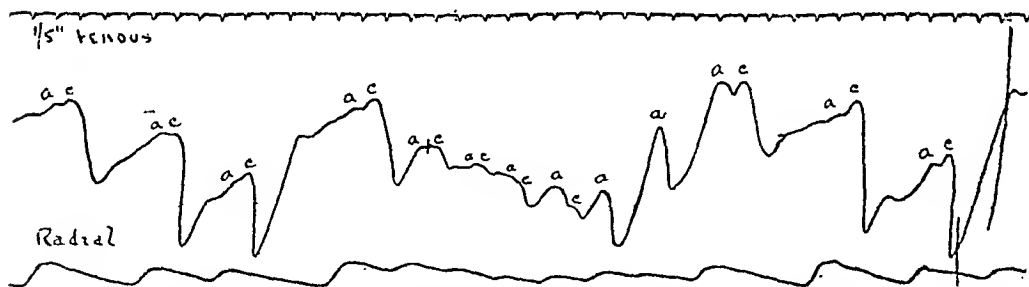


FIG. 2. A paroxysm of seven beats at the rate of 140 per min., terminating in a pause of about the same length as the compensatory pause after the extra-systole which precedes the attack.

trigeminal type; that is to say, there is an auricular extra-systole after every single or every second normal beat. This is noteworthy for its persistence. For the past three months when the patient is standing or sitting the pulse has been almost constantly of the bigeminal type. Exertion and emotion in temporarily quickening the pulse disturbs this rhythm, but the bigeminal quickly returns. When, however, the patient lies down the rhythm becomes less regular, the bigeminal rhythm is not so persistent, and a trigeminal appears with a slight degree of sinus arrhythmia. When the paroxysms are more frequent the pulse in the intervals is for the most part of the trigeminal type, with slight sinus arrhythmia when the former rhythm is interrupted. All the extra-systoles hitherto observed in this patient have been of auricular origin. The pause

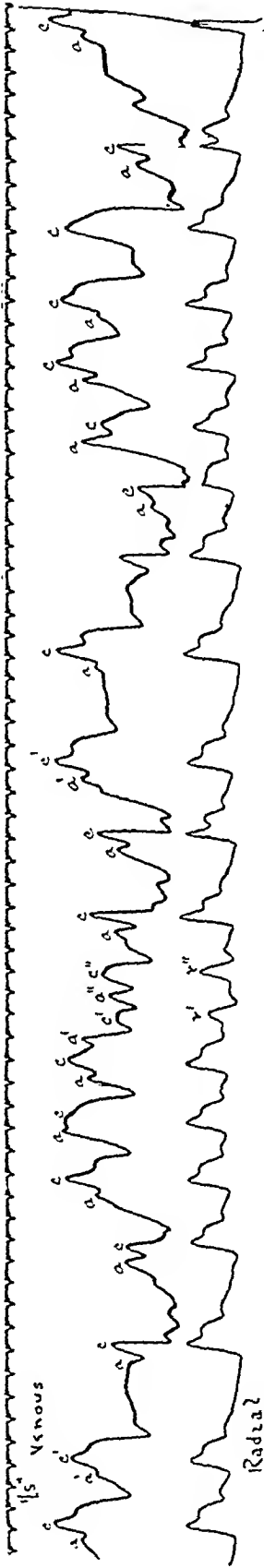


FIG. 3. Shows two short paroxysms. The first terminates by two auricular extra-systoles. The offset of the second is gradual.

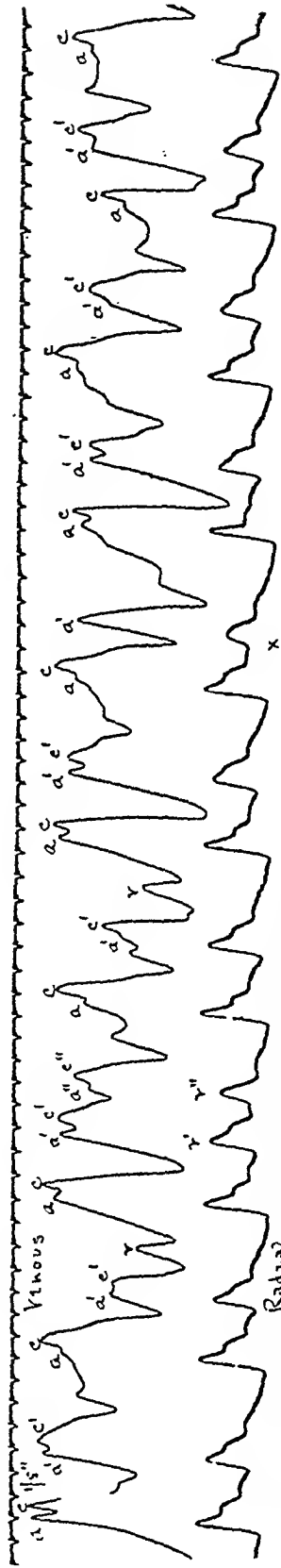


FIG. 4. Continuous pulsus bigeminus. It is interrupted once by a second auricular extra-systole, and the corresponding compensatory pause is shortened. The normal pulse periods are constant, although at X the auricular extra-systole occurs earlier than elsewhere.



paroxysm in Fig. 3. Here the rate diminishes gradually so that it is not easy to say with certainty where the paroxysm ends. The fifth pulse period is equal to a rate of 82 per minute and this is followed by a long pause. A gradual offset in this way is not usual in this patient. On several occasions when paroxysms were frequent there was a series of three to five regular beats at a rate of 96-100 per minute, followed by a long pause. Such may be instances of sinus arrhythmia, but in the absence of electro-cardiograms it cannot be decided with certainty. The occurrence of such beats is of interest in connexion with the gradual offset of a paroxysm just considered.

Lewis has come to the conclusion that there is no essential difference between extra-systolic and paroxysmal beats when of auricular origin. They may perhaps differ in the exact site of the impulse formation. The present case, therefore, like the one he studied, forms a connecting link between cases in which there are single ectopic beats and others in which ectopic rhythms of long duration occur. Paroxysmal tachycardia which is due to ectopic impulse formation may arise at various levels of the heart. From a recent paper by Marris it appears that paroxysms of tachycardia may be generated from at least two different foci in the auricular tissue in one and the same subject. For at one time the patient considered had paroxysms of tachycardia which were probably of atrio-ventricular origin (Lewis), while at another time they were of distinctly auricular origin.

#### REFERENCES

- Cowan, McDonald, and Binning, *Quart. Journ. Med.*, Oxford, 1908-9, ii. 146.  
Hay, *Edin. Med. Journ.*, 1907, N. S., xxi. 42.  
Hirschfelder, *Johns Hopkins Hosp. Bull.*, Balt., 1906, xvii. 337.  
Lewis, *Heart*, Lond., 1909-10, i. 43.  
Lewis, *Ibid.*, 1909-10, i. 262.  
Lewis, *Ibid.*, 1909-10, i. 306.  
Marris, *Heart*, Lond., 1910, ii. 74.  
Schmoll, *Amer. Journ. Med. Sci.*, 1907, N. S., cxxxiv. 662.

# MODERN ENGLISH CARDIO-VASCULAR TEACHING: A REJOINDER

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With Plates 28 and 29

It is customary for those who make a special study of graphic records to give, when explaining their figures, interpretations of the curves which appear to them in closest accordance with previously published facts, and with their own experience of similar curves.

In giving dogmatic interpretations of curves, a conscientious writer confines himself to such interpretations as he feels will meet with the general approval of those who are alone fitted to judge of their correctness. I speak of those who are actively engaged in the collection of facts. He is not called upon to repeat, in each instance, the evidence which is well known to such students, though it may be unknown to the casual inquirer, but only to give a sufficiency of evidence to make his whole communication rational. It so happens that any who may chance upon isolated examples of curves, the interpretation of which appears to stand in contradiction to their own preconceived ideas, are entering upon a hazardous course when they venture to criticize before rendering themselves fully conversant with the facts.

It is not my purpose to follow Dr. Brockbank from paragraph to paragraph, or to show, as could be shown, the tenuity of one argument after another as they are advanced in his article. It is not the duty of a worker to defend the writings of a school to which he may be thought to belong; but it is his right to vindicate those personal interpretations of his published curves, which have been called in question.<sup>2</sup> This I shall proceed to do.

The first tracing to which I wish to refer is the first figure of Dr. Brockbank's article (republished from *Heart*, 1909-10, i. 48, Fig. 1). It is again published, as Fig. 1 of this communication. Dr. Brockbank says of it (this *Journal*, 1910, iii. 349):—

'Here are jugular and radial pulse records from a patient with a pulse rate of 187, and it is said that the *a-c* interval was *equal to or slightly more than* 0.02 sec.—certainly it measures this by the time marks. It will be seen that the *a* wave is very prominent, and if perpendiculars be drawn from its origin and from its summit they will be found to enclose a space

<sup>1</sup> Working under the tenure of a Beit Memorial Research Fellowship.

<sup>2</sup> And in so doing I shall answer the criticisms, not only of the interpretations of my own curves, but also of many others which are discussed in Dr. Brockbank's paper.

equal to full 0.20 sec. So here we have a figure showing that out of 0.3 sec. occupied by the whole of the cardiac cycle, not only does the *a-c* interval equal 0.2 sec. or more, but auricular systole itself extends throughout the whole of this period of time, and that is more than twice the time that is occupied by ventricular systole. In other words, whilst the duration of ventricular systole is normally about three times as long as auricular systole, here it is half as long, or one-sixth of its normal relative duration as compared with auricular systole.'

Dr. Brockbank concludes that if the interpretation of the curve is correct the auricular is of twice the duration of ventricular systole, and appeals to the incredulity of his reader on this ground. But on what evidence does he base his contention?

First, it is based upon a calculation of the length of auricular systole. The measurement is made by Dr. Brockbank *by drawing perpendicular lines from the origin and summit of the wave a*. Now let us assume for the sake of argument that the base and summit of *a* are representative of the times of onset and offset of systole in the auricle, an assumption which, though knowing *a* to result from auricular systole, I never have made. Is the measurement which Dr. Brockbank makes justified? It is anything but justified, and entails an

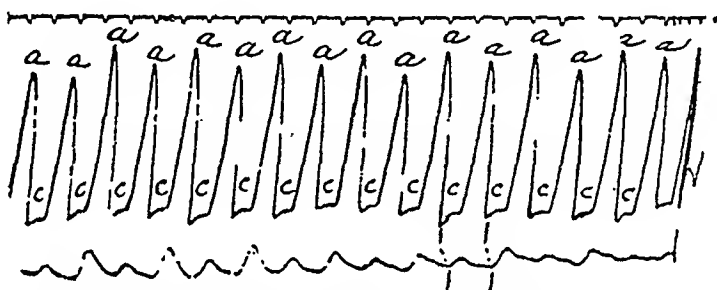


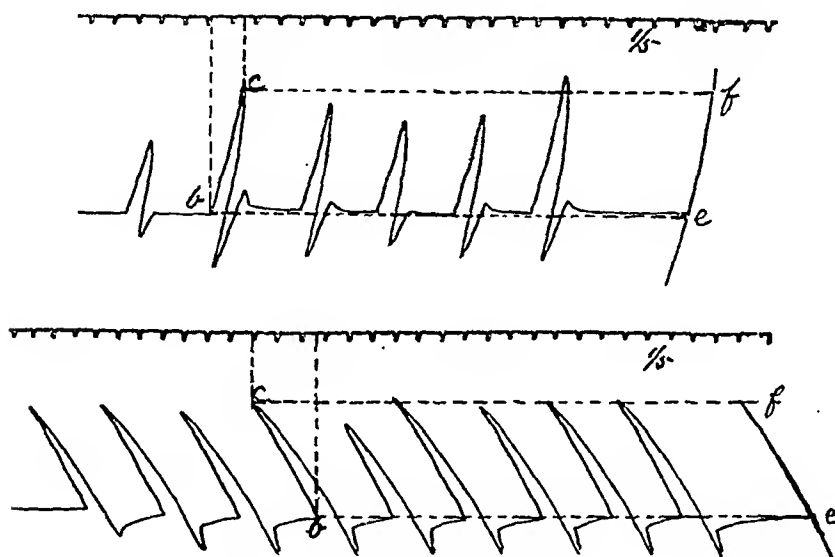
FIG. 1. A polygraphic curve from a case of paroxysmal tachycardia, in which, while ventricle is responding to auricle, a given auricular systole coincides with the end of the preceding ventricular contraction. The first curve criticized by Dr. Brockbank.

extremely elementary blunder. The curve is written from left to right by a lever, the pen of which moves through the arc of a circle. Any transference of times from points of the curve which lie at different levels on the paper has to be corrected against the index-mark which is shown at the end of the curve, and this index-mark is not perpendicular. The general direction in which the pen inclines, in writing the *a* waves measured, is of first importance if the smallest approach to accuracy is to be obtained in measurement. Let me take an extreme case. I have drawn two series of waves with a polygraphic lever on separate strips of paper, on each of which the time is marked in fifths; and I have lettered the waves *b* and *c*. Each strip also shows its respective index-mark, but they are at different inclinations. The waves in Figs. 2 and 3 are of approximately the same dimensions. Following the example of Dr. Brockbank, let us draw perpendiculars from *b* and *c* to the time marker in each curve. We know at the outset that the actual time distance between *b* and *c* is approximately the same in the two curves, for they were drawn in a similar manner. In Fig. 2 it measures, by the method of perpendiculars,  $\frac{1.4}{5}$  sec. (the

time marker is in  $\frac{1}{5}$  sec.). In Fig. 3 it is a minus quantity; the actual measurement stands at  $-\frac{2.6}{5}$  sec. According to the angle at which your lever writes, you make the length  $b-c$  what you please. How is the true measurement of the time interval between points  $b$  and  $c$  to be obtained? By very simple means. It is found by subtracting the distance  $c-f$  from the distance  $b-e$  (Figs. 2 and 3).

The true measurement of the time interval between the origin and summit of the  $\alpha$  waves in Fig. 1 is somewhat less than 0.1 second, or less than half the distance given by Dr. Brockbank.

Let us turn to the second measurement of the same writer. He states that of 0.3 sec. occupied by the whole cardiac cycle, 0.2 sec. is taken up by the



FIGS. 2 and 3. Two series of curves drawn with the polygraph. The curves are quite roughly drawn, but are sufficient for purposes of illustration. At the end of each series, the curved index-marks are shown. It will be observed that they are inclined in different directions. The general inclination of the waves is the same as that of the corresponding index-mark. To illustrate the fallacy of measuring the duration of waves by drawing perpendiculars to the time marker.

auricular systole. And he infers therefore that ventricular systole cannot occupy more than the remainder, namely 0.1 sec. In taking this second step, Dr. Brockbank utilizes a time measurement (e. g. 0.2 sec. for auricular systole) which is absolutely invalid. If any measurement had been taken it should have been, as we have seen, 0.1 sec. The relationship of what he chooses as measurements of auricular and ventricular systole would then have stood at 0.1 sec. for auricular and 0.2 sec. for ventricular systole respectively. In brief, whereas he infers that my interpretation shows auricular to be twice the duration of ventricular systole, he should, in taking the second step, have allowed the reverse relationship. But this does not complete a description of the errors in the complete argument. It is assumed that as the pulse rate is 187, the length of the whole of each regular cardiac cycle is 0.3 sec. The value of the whole cardiac cycle is



apparently obtained by the not very exact calculation  $\frac{60}{187} = 0.3$  (I note in passing that the inexactitude tells in favour of Dr. Brockbank's thesis). But as a matter of fact the foundation of the whole argument is fallacious. It is quite beyond the bounds of possibility to calculate the length of 'a whole cardiac cycle' by an estimate of pulse rate. All that can be deduced in regard to the lengths of systole of auricle and ventricle from a pulse rate of 187 is that ventricular systole occupies less than 0.32 seconds. And the reason for this is obvious, for it may chance that auricular and ventricular systole coincide. I illustrate

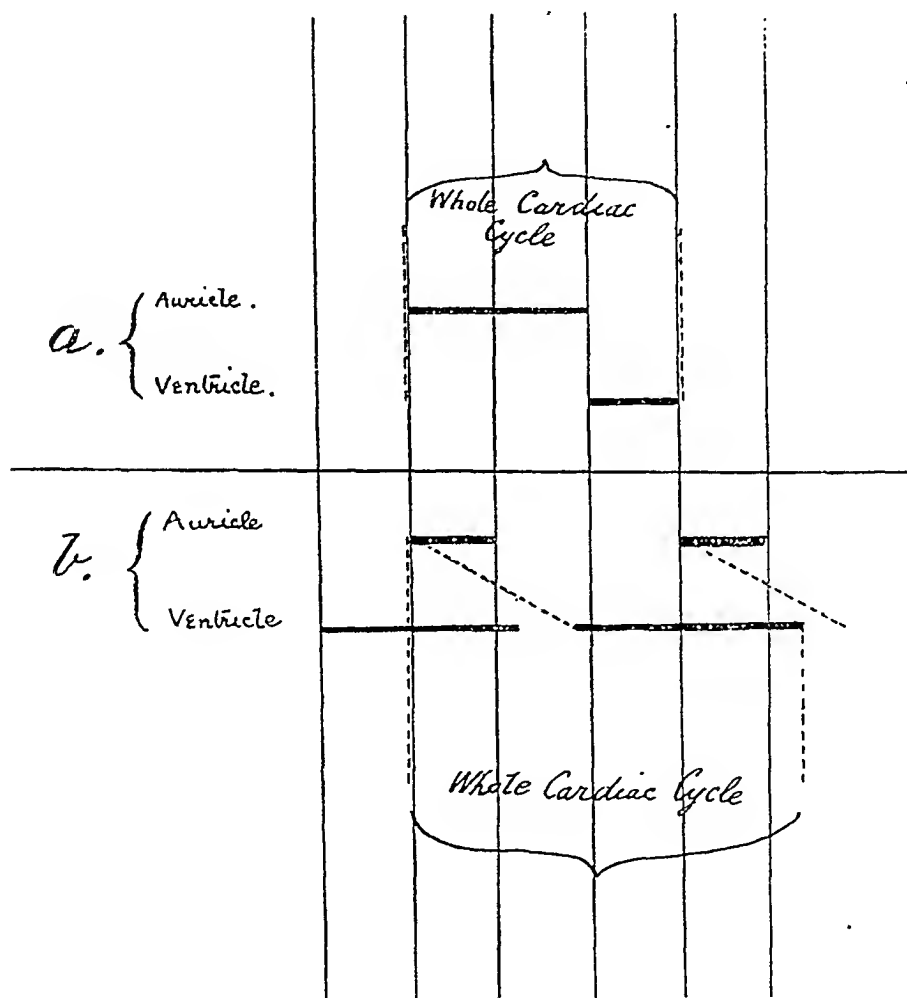


FIG. 4 *a* and *b*. Two figures illustrating interpretations of the mechanism portrayed by Fig. 1. The vertical lines are separated by time intervals of 0.1 sec. The figures show the fallacy of calculating the length of the 'whole cardiac cycle' from the pulse rate.

this point by the accompanying diagram. Fig. 4 *a* depicts cardiac cycles in which the relationships of auricular and ventricular systoles is as Dr. Brockbank would have them. Fig. 4 *b* depicts a relationship such as I maintain is far more probable for the case under consideration. And Dr. Brockbank deliberately neglects this question of coincidence of systoles in referring to my figure, although such coincidence is spoken of in perfectly distinct language in my original paper (p. 49).

I submit that instead of the statement that 'out of 0.3 sec. occupied by the whole of the cardiac cycle, not only does the  $a-c$  interval equal 0.2 sec. or more, but auricular systole itself extends throughout the whole of this period of time, and that it is more than twice the time that is occupied by ventricular systole', Dr. Brockbank should have written, 'the auricular systole occupies 0.1 sec. or less,'<sup>3</sup> and as the ventricular cycle cannot be shown to be shorter than 0.25 sec., it is beyond my power to demonstrate from the original interpretation of this figure that auricular systole is more than  $\frac{1}{2}$  to  $\frac{1}{3}$  the length of ventricular systole.' The deviation between actual and justifiable statement is sufficiently conspicuous to require no further comment.

I pass to the second of my published curves, the interpretation of which is the subject of Dr. Brockbank's remarks. It stands as Fig. 6 in his paper, and the original will be found in this Journal, 1908-9, ii. 359 (Fig. 6). I reproduce it here again, as Fig. 5.

Now I maintain in the first place that it is illegitimate to separate a tracing from its companion curves, and it happens that the isolation of this particular example materially detracts from its value. The curve in question is one of a group of seven published from the same case, and of the two curves criticized (Figs. 6 and 7 of the original paper) Fig. 6 is alone republished by Dr. Brockbank. I republish Fig. 7 also (it stands as Fig. 6 of the present paper).

In regard to these two figures, Dr. Brockbank writes (pp. 353-4):—

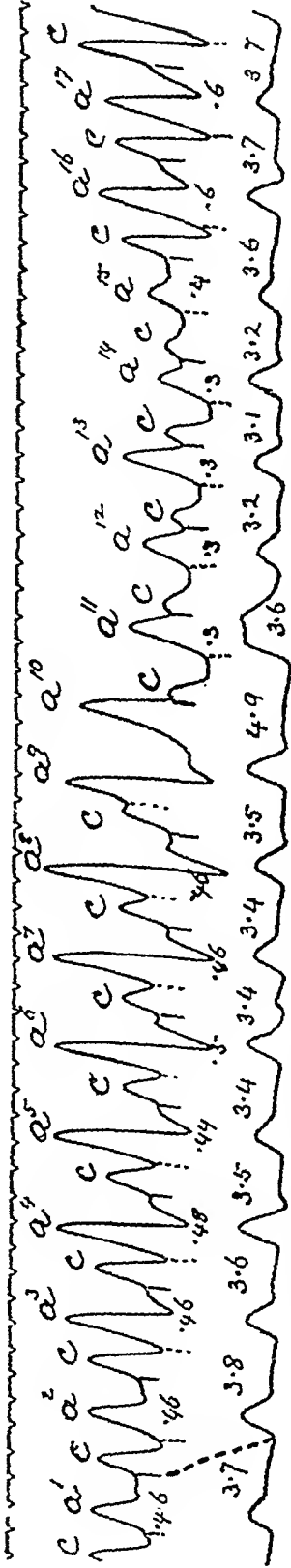
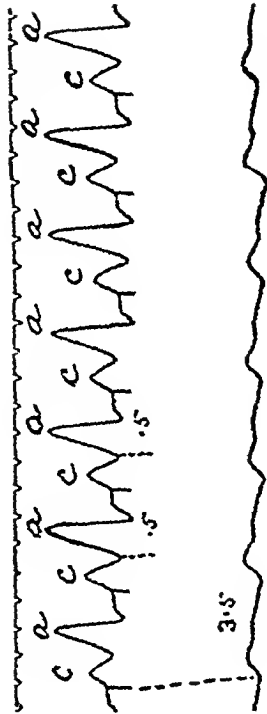
'Another illustration of the passing over of waves which, occurring at the proper time, are possibly, if not probably, due to auricular systole, occurs in a paper by Lewis in this Journal on "Irregular Action of the Heart in Mitral Stenosis and the inception of Ventricular Rhythm". In Figs. 6 and 7 the wave marked  $a$  and attributed to auricular systole, without any obvious reason, is, I suggest, wrongly marked. In Fig. 6<sup>4</sup> there is a distinct wave at the proper time for that due to auricular systole and following, by as much as 0.30 sec. in some beats, the wave attributed in the tracing to auricular systole. In Fig. 7<sup>5</sup> again the wave marked  $a$  precedes by 0.25 sec. a distinct wave at the proper time for auricular systole.'

Now take the first curve referred to, Fig. 5 of this paper. I recognize that it would perplex me to show on *the evidence of this curve alone* (and it is the only curve republished by Dr. Brockbank), and to an uninitiated reader, that the wave marked  $a$  is the true representative of auricular systole. But I shall have no difficulty in showing that such is the case if I am allowed to refer to other curves taken from the same patient. Fig. 6 was taken at the same sitting and was published at the same time. There are waves in this figure of a similar nature. I have marked certain waves  $a^1-a^{17}$  respectively and I direct attention to  $a^2$  and  $a^{16}$  especially. I think there can be no doubt, even amongst the most sceptical, that the waves marked  $a^2$  and  $a^{16}$  in Fig. 6 have been caused by a similar mechanism to that which produced the waves marked  $a$  in Fig. 5.

<sup>3</sup> Personally I will not state its length at all.

<sup>4</sup> Fig. 5 of the present paper.

<sup>5</sup> Fig. 6 of the present paper.



Figs. 5 and 6. Two criticized curves originally published in this Journal. Fig. 5 was republished in Dr. Broetbank's article and stands as Fig. 6 of his paper. The curves were originally described to demonstrate the presence of heart-block in the case from which they were obtained. The heart of the patient has recently been examined and shows extensive damage to the auriculo-ventricular bundle. They are companion curves and are fully described in the text. They illustrate the danger of separating such companion curves. The one curve explains the other.

But in Fig. 6  $a^2$  and  $a^{16}$  stand in definite relationship to the full series of  $a$  waves shown. They fall at approximately equal distances throughout the whole curve, though they vary in form. It is the relationship to the preceding ventricular systole, represented by  $c$  in the upper or venous curve, which shows variation in time, and this, as we shall see, is the cause of the variation in the form of the whole series of waves marked  $a$  in the curve considered (details which are fully entered into in my original paper and which I must perforce repeat). My contention is that the waves marked  $a$  in the curve are due to auricular systoles. Take  $a^{11}$  and  $a^{12}$ : they are *prominent* waves immediately preceding the  $c$ 's, the representatives of the onsets of corresponding ventricular contractions. They stand in the presystolic periods of the jugular curves, and there is no factor in operation in the heart, other than auricular systole, and at such times, which is capable of giving rise to waves of this kind. They are not in any way attributable to a ventricular systolic event, for ventricular systole has terminated before each of such waves commences. And if this could not be shown in the case of  $a^{11}$  and  $a^{12}$ , it would be obvious in the case of  $a^{10}$ , which stands, as the radial curve shows, at the end of a relatively long diastole. Now a curious transition is shown between  $a^{11}$  and  $a^{17}$ . The interval between  $a^{11}$  and its corresponding or succeeding  $c$  is 0.3 sec.; and this interval is maintained for four beats. At  $a^{16}$  there is further prolongation of the interval (the normal length is 0.2 sec. or less) to 0.4 sec. and in the succeeding beats the value reaches 0.6 sec. Yet the waves marked  $a$  are approximately regular throughout. The variation in intervals is an accompaniment of a movement of a given ventricular contraction ( $c$  wave) away from the wave  $a$  of the corresponding cycle. And this delay of ventricular contractions is necessarily followed by a gradual approach of a given  $a$  wave to the preceding ventricular contraction. Now what is the rational interpretation of these events? It is that the  $a$  waves are due to auricular systole and that the auricular systoles are the cause of the succeeding ventricular contractions, but that for some reason or other there has been an increasing impediment to the passage of the impulses supplied to the ventricle by auricular contractions; thus, as the curve proceeds, the auricular systole and the corresponding ventricular response become further removed from each other. Now this interpretation is in complete accord with a host of researches of the most careful kind, and well known to special students of the subject. But let us continue to examine the proposition on its own merits, in respect of the curves shown. An examination of waves  $a^{11}$  to  $a^{17}$  leads us to the conclusion that there is a defect in the conduction of impulses from auricle to ventricle. This conclusion is in absolute agreement with the interpretation of the events surrounding  $a^9$  and  $a^{10}$ .  $a^9$  is followed by no radial beat, neither is there a  $c$  wave following it in the phlebogram.<sup>6</sup> On the other hand it is associated with an increased pause in the radial pulse. This pause is attributed to

<sup>6</sup> The venous lever is not writing directly above the radial curve but somewhat to the left of it. Corresponding arterial pulsations are joined by a dotted line at the beginning of the curve.

a 'dropped beat', an exaggeration of the impediment to the passage of impulse already noted, an exaggeration which culminates in a complete failure of response. Lastly, we may revert to the question of the variation in height of the waves marked  $a$ . This variation receives complete explanation, if it is assumed that the  $a$  waves are the result of auricular systoles. For the height of a given wave is in proportion to the calculated pressure at the tricuspid ring at the moment of its occurrence. The nearer the approach of an  $a$  wave to the preceding  $c$  wave, the higher it is; and this is so for the reason that the auricular contraction falls further and further into the preceding ventricular systole, and that instead of the auricle emptying into the ventricle its contraction tends to raise venous volume. The phenomena of coincidence of auricular and ventricular contraction, and exaggeration of the wave in the phlebogram with which such coincident contraction is associated, have received accurate experimental study by several observers, and are perfectly well recognized. It is beautifully illustrated in the two venous staircases shown in Fig. 6. (The exaggeration of  $a^{10}$  is the outcome of the increased pressure in the ventricle as the result of blood accumulation in it during the long diastole.)

Now I contend that this interpretation of Fig. 6 is absolutely in accord with previously published *facts*, that the proposition that the  $a$  waves are the result of auricular systoles constitutes the only rational interpretation of the curve, and this interpretation would be unhesitatingly adopted by any one sufficiently acquainted with polygraphic work. The reading of the figure gives unquestionable evidence of the presence of heart-block, evidence in every way compatible with our knowledge of heart-block. But if the  $a$  waves of Fig. 6 are due to auricular systoles, so are also the  $a$  waves of Fig. 5, for they may be traced continuously in the original curves from one tracing to the other. In Fig. 5 the interval  $a-c$ , as marked, is increased (from the normal 0.2 sec.) to 0.5 sec.

Dr. Brockbank's chief difficulties in regard to Fig. 5 are, first, his unwillingness to admit the possibility of a widened conduction interval, and secondly, his failure to appreciate the possibility of the coincidence of an auricular with the preceding ventricular contraction.

To each of these questions I shall return subsequently. At the present time let it be noted that I published these two figures with a specific object, namely, to demonstrate the presence of impairment of impulse conduction between auricle and ventricle, a demonstration which Dr. Brockbank will not allow to have been completed. Now impulse conduction from auricle to ventricle occurs, as my readers will know, through a narrow bridge of tissue uniting auricle to ventricle, the auriculo-ventricular bundle. The sequel speaks for itself. As a result of an examination of these curves, I was of opinion that the functions of this bundle were deficient, and the curves were published as evidence of the contention. The patient from whom the curves were taken died many months ago,<sup>7</sup> and Professor Woodhead reports that the bundle in question is invaded by a conspicuous lesion. So much for the actual curves and the

<sup>7</sup> The heart's mechanism remained practically unaltered until death occurred.

conclusions to be drawn from them. I turn to a further demonstration of two facts: (1) that while ventricle is responding to auricle, the auricular systole may coincide with the preceding ventricular contraction, and (2) that a prolongation of the interval between  $a$  and  $c$  waves in the jugular pulse is an invaluable and sufficiently accurate guide to the interval between the onset of auricular and ventricular systoles in the heart itself.

The first demonstration is necessitated, because I utilize the argument in the discussion of Figs. 1, 5, and 6, and because Dr. Brockbank is disinclined to admit it; he neglects the possibility where he calculates the relative duration of auricular and ventricular systoles (cf. Fig. 4 and discussion relating to it).

The second demonstration is necessitated while Dr. Brockbank, in speaking of heart-block, writes (on p. 359):—

‘Such cases’ undoubtedly exist, but there is no definite clinical evidence to show that the  $a$ - $v$  bundle ever passes on stimuli at a pathologically slow rate, let alone at such an abnormally slow rate as it is said to in Griffith’s and Lewis’s cases.

A prolongation of the  $a$ - $c$  interval in hearts beating 60 or 40 or less is quite conceivable in cases of mitral stenosis or disease of the  $a$ - $v$  bundle, without there being any alteration at all in the normal sequence of events of a cardiac cycle.’

Now whatever be the merits or demerits of the polygraphic method, I think that even Dr. Brockbank will be prepared to admit that we have in the electro-cardiographic method a certain means of identifying the approximate times of onset of auricular and ventricular systole. It is a method of recognized accuracy and is in no way open to criticism on the score of variation in transmission intervals. After a large experience of both methods, I have no hesitation in stating that the galvanometer has confirmed all the main and generally recognized facts which have been won by the polygraph; these new records have completely substantiated the value of the older method.

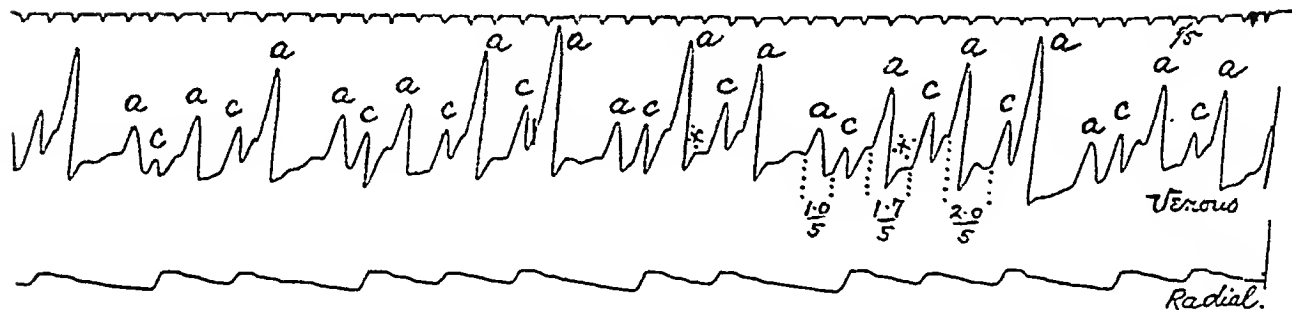
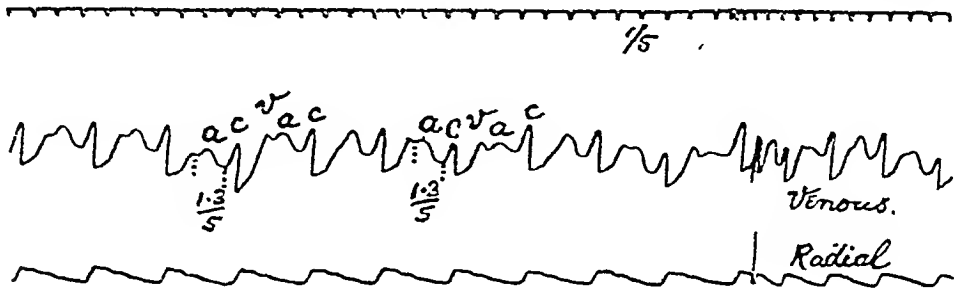
When I enter upon a demonstration of the two propositions cited above, I do so under protest. I say emphatically that both these propositions were established before the modern electro-cardiogram was heard of.

The fact that a prolongation of the auriculo-ventriculo-systolic interval may occur has been fully established experimentally, and I should have no difficulty in quoting abundantly to this effect. But let us confine ourselves to the mammalian heart with which we are dealing. It will suffice if I quote from Erlanger’s classical paper on this subject. Speaking of the dog’s heart, he says (*Journ. of Exper. Med.*, 1906, viii. 57):—

‘(1) Upon cautiously tightening the clamp, the first obvious effect may be an increase in the period intervening between the beginning of an auricular contraction and the beginning of the ventricular contraction, the *intersystolic period*, of the same cardiac cycle. The duration of the intersystolic period may then gradually increase in the successive cycles until eventually the ventricles fail to respond to one of the auricular contractions (Fig. 20,  $\sigma$ ). Immediately following this ventricular “silence” the intersystolic period again becomes short and it again increases,’ &c.

But it is my desire that the reader should have the actual facts before him. In Figs. 9 and 10 I reproduce electro-cardiographic curves, taken from two dogs

during periods of asphyxia (Lewis and Mathison, *Heart*, 1910-11, ii. 47, Figs. 2 and 3). The normal electro-cardiogram consists of three chief summits, P, R, and T, and in regard to these peaks it has been shown beyond dispute that P represents auricular and R and T ventricular contraction. The two figures, which are republished, show partial heart-block. Each ventricular complex (R, T) is preceded by an auricular peak, P, but at very varying time intervals. And in two places in the first figure (Fig. 9) and in three places in the second figure (Fig. 10) a P summit stands isolated. The responses to these auricular beats are 'dropped'. After each dropped beat there is a prolonged ventricular



FIGS. 7 and 8. Two polygraphic curves from a case presenting signs of regurgitation through the mitral orifice. They show prolongation and variation of the *a-c* interval; and are published for this purpose. In Fig. 7 the *a-c* interval is  $\frac{1.3}{5}$  sec. In Fig. 8 there are 'dropped' beats.

pause, at the termination of which the interval P-R (a measurement of the auriculo-ventriculo-systolic period) is relatively short. With the succeeding beats it shows gradual prolongation, i.e. the auricular impulses are transmitted, with ever increasing difficulty, up to the point where response fails. The events in Fig. 9 are as follows:—P-R interval 0.12, 0.14, 0.17, dropped beat. In Fig. 10 they are P-R interval 0.13, 0.18, 0.30, dropped beat.

Again, note the position of the P waves, which are succeeded by long intervals; they fall within the limits of preceding ventricular systoles, for ventricular systole ends somewhat later than the point at which the broad T wave reaches the base line.

Let us turn to the final demonstration, for Dr. Brockbank, though prepared to quote experimental evidence, specially mentions the *clinical* evidence.

Figs. 7 and 8 were taken from a single patient,<sup>9</sup> a case of exophthalmic goitre with enlargement of the left ventricle and mitral regurgitation. They are polygraphic curves and are selected from a series taken from this patient. The curves as a whole showed, from day to day, a gradual and uniform improvement in auriculo-ventricular conduction, which was considerably damaged when the patient was first seen.

The phenomena noted in this patient were as follows:—

First day of observation: ventricle responding to each second, and occasionally to each third auricular contraction only.

Second day: ventricle responding to each second auricular contraction, and occasionally to successive impulses.

Third day: ventricle responding to successive auricular contractions, with occasional dropped beats.

Fourth and subsequent days: prolongation of the auriculo-ventriculo-systolic interval; no dropped beats.

I begin with the later curves. Fig. 7 is from a prolonged tracing in which the  $a-c$  interval measures  $\frac{1.3}{5}$  sec.<sup>10</sup> It is given for comparison with a simultaneous polygraphic and electric curve taken on the preceding day. This is shown in Fig. 11. In the electro-cardiographic and venous curves regularly placed waves are seen:—

	<i>Auricle</i>	<i>Ventricle</i>
<i>Electro-cardiographic</i>	P	R, T
<i>Polygraphic</i>	<i>a</i>	<i>c, v</i>

In the electro-cardiographic curve the P-R distance, in the venous curve the  $a-c$  distance, is taken as an index of auriculo-ventricular conduction. Now the curve reads from left to right, and  $c$  stands approximately  $\frac{0.6}{5}$  sec. to the right of R and  $a$  approximately  $\frac{0.6}{5}$  sec. to the right of P. This interval is due in part to the conduction time of the venous waves to the neck, and in part to the transmission time of the recording apparatus (calculated at the time at  $\frac{0.2}{5}$  sec.).<sup>11</sup> The figure shows a series of  $a-c$  and P-R interval of  $\frac{1.4}{5} - \frac{1.5}{5}$  in duration. The divergence between  $a-c$  and P-R is in no instance greater than  $\frac{1}{50}$  sec., a divergence well within the limits of technical error. Now I am far from saying that the correspondence is always so clear, but it is necessary to emphasize the fact that there is never a wide divergence, and that

<sup>9</sup> For the opportunity to examine whom, I am indebted to Mr. Wilfred Trotter.

<sup>10</sup> I give the measurements in this form because the time marker is in  $\frac{1}{5}$  sec. The figure above the line gives the number of fifths.

<sup>11</sup> It is also due in part to the fact that the electric effect slightly precedes the actual contraction.



as a result of the comparison in a number of cases, it may be affirmed that where the  $a$ - $c$  interval exceeds  $\frac{1}{5}$  sec., the P-R interval will be found to have increased, and speaking of practical measurements, the prolongation is of approximately equal extent in both. There can be no question from Fig. 11 not only that the auriculo-ventriculo-systolic interval may be prolonged, but that in certain instances the auricular systole ends long before the ventricular systole starts.

We go back to the earlier but more complex curves. Figs. 12 and 13 are from the same case, but the grade of block is higher. There are dropped beats and the P summits are often falling during the limits of preceding ventricular systoles. The positions of these coincidental beats are marked by dotting the outlines of the T variations in white beneath the composite curves. Where P and T fall together, the former is found by subtracting the known outline of T from the whole summated curve. The events portrayed in Fig. 12 may be compared with those of Figs. 9 and 10, for they are exactly parallel. The phenomena are represented as follows:—

P-R interval  $\frac{1.2}{5}$ ,  $\frac{1.5}{5}$ ,  $\frac{1.8}{5}$ , dropped beat.

Again, take Fig. 8 (a polygraphic curve obtained on the same day). It shows events which are parallel to those of Fig. 6, the criticized curve. Beats are dropped after each second or each third response; and there is a widening of  $a$ - $c$  intervals ( $\frac{1.0}{5}$ ,  $\frac{1.7}{5}$ , and  $\frac{2.0}{5}$ ) up to the dropped beat. Note also the rise in the height of  $a$  as it falls back further and further towards the preceding  $c$ .

In Fig. 13 I publish another curve taken from this patient on the same day, simultaneous electro-cardiographic and polygraphic tracings, which should lay all doubts of interpretation at rest. The strip may be compared with that part of Fig. 8 in which the intervals are marked. In Fig. 13 each R summit is followed by a  $c$  wave in the venous curve, while each summit is succeeded by a wave marked  $a$  (the separation of  $a$  and P or  $c$  and R is approximately by the usual interval,  $\frac{0.6}{5}$  sec.). Now in Figs. 7 and 11 the  $a$  waves are small, and for the reason that auricular and ventricular systoles ( $a$  and  $v$  or P and T) do not coincide, while in Fig. 13 the characteristic staircase of  $a$ 's ( $a^1$  to  $a^4$ ) is shown as each successive  $a$  falls further back towards the preceding  $c$ . The practical interpretation of the curves as a whole is complete; they are proof against the greatest scepticism. But, says Dr. Brockbank (p. 354), in referring to Fig. 5:—

'there is a distinct wave at the proper time for that due to auricular systole and following, by as much as 0.30 sec. in some beats, the wave attributed in the tracing to auricular systole.'

I draw Dr. Brockbank's attention to the similar waves in Figs. 8 and 13, waves marked with asterisks, and ask him if by any effort of imagination he can attribute them to an event synchronous with the onset of auricular systole. They fall approximately 0.26 sec. later than the wave marked  $a$  in this instance. To what are they due? I leave Dr. Brockbank to decide: they are

of little consequence to those of us who look to a practical issue of our observations, for we know from the simultaneous electric curves that the *a* waves marked are due to auricular systoles.

Let me sum up the position. Dr. Brockbank has thought fit to criticize certain published curves. His criticisms are totally invalid. He has attempted to cast doubts upon the interpretation of certain events and certain deductions made from them. The interpretation as originally stated is justified by a careful analysis of the curves themselves, and the conclusions are upheld by an abundance of evidence.

At the present time we are face to face with a mass of new facts, and with problems of considerable complexity. It is not the time for controversy, it is the time for patient endeavour in the collection and sorting of these facts. It is necessary to impress upon my readers that those of us who are intent upon arriving at the meaning of these new facts can ill afford to turn aside from the legitimate path of investigation to reply to criticisms which have no real foundation. And I may be permitted to state once more my emphatic opinion, that if criticism is to be of service, it must come from those who are taking an active part in building up the real knowledge of the subject.

## DESCRIPTION OF FIGURES.

PLATE 28, FIGS. 9 and 10. Two electro-cardiograms from separate dogs during periods of asphyxia. P represents auricular and R and T ventricular systole. They show that prolongation of the auriculo-ventriculo-systolic interval occurs in experiment, and that an auricular contraction which originates a ventricular response may fall back upon the preceding ventricular systole.

PLATE 28, FIG. 11; PLATE 29, FIGS. 12 and 13. Electro-cardiographic curves and poly-graphic curves from the same case as Figs. 7 and 8. They show in the most conclusive manner that the interpretation of Figs. 7 and 8 is correct; and prove beyond question that clinically auricular and ventricular beats may coincide, where ventricle is responding to auricle, and that prolongation of the auriculo-ventriculo-systolic interval occurs in man. It should be remembered that the curves are but short sections of prolonged tracings. The same series of events was repeated time after time. Time as in all curves is in  $\frac{1}{5}$  sec.

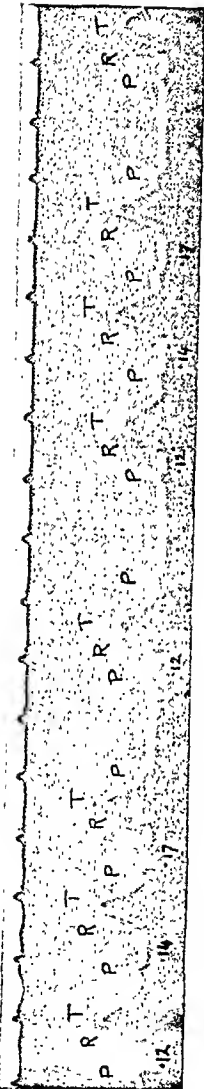


Fig. 9

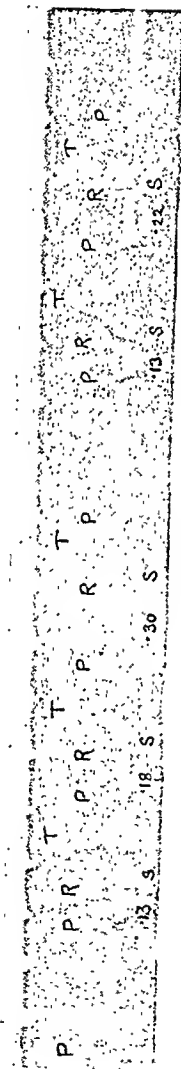


Fig. 10

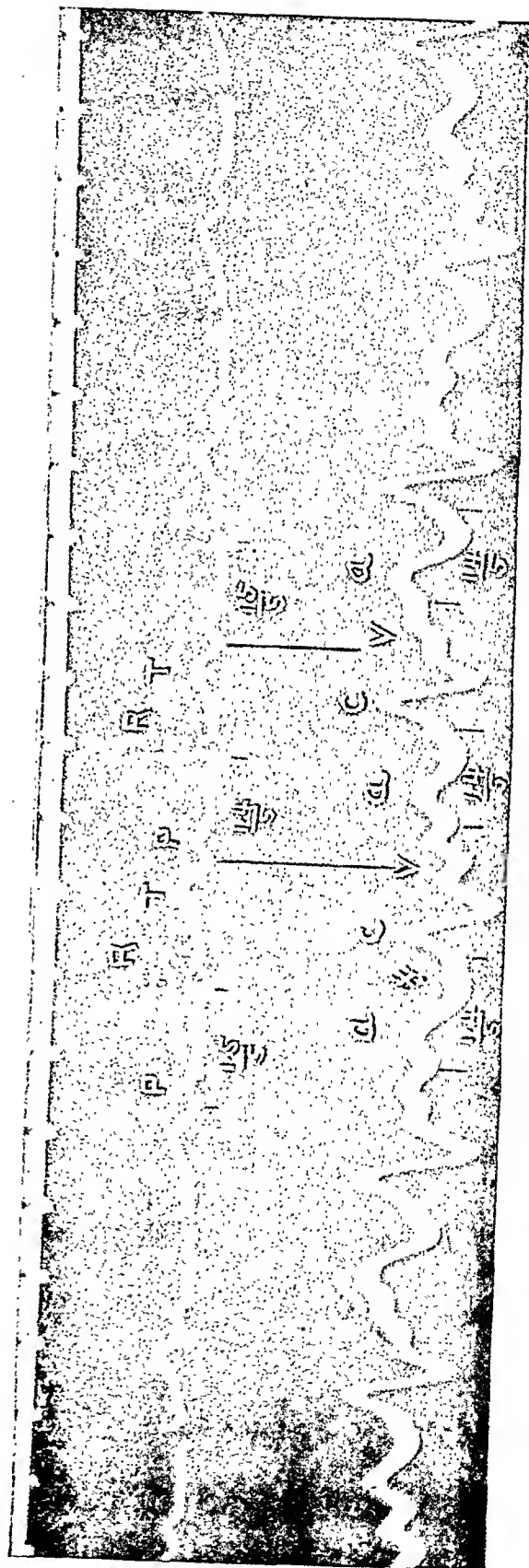


Fig. 11



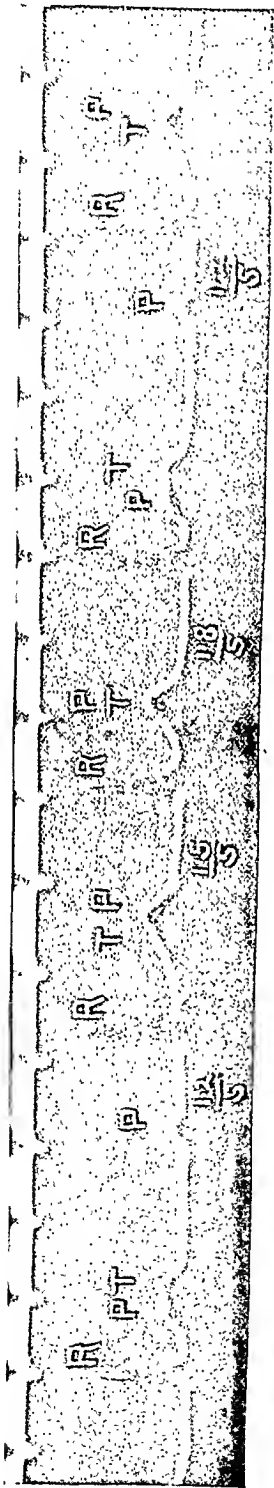


FIG. 12

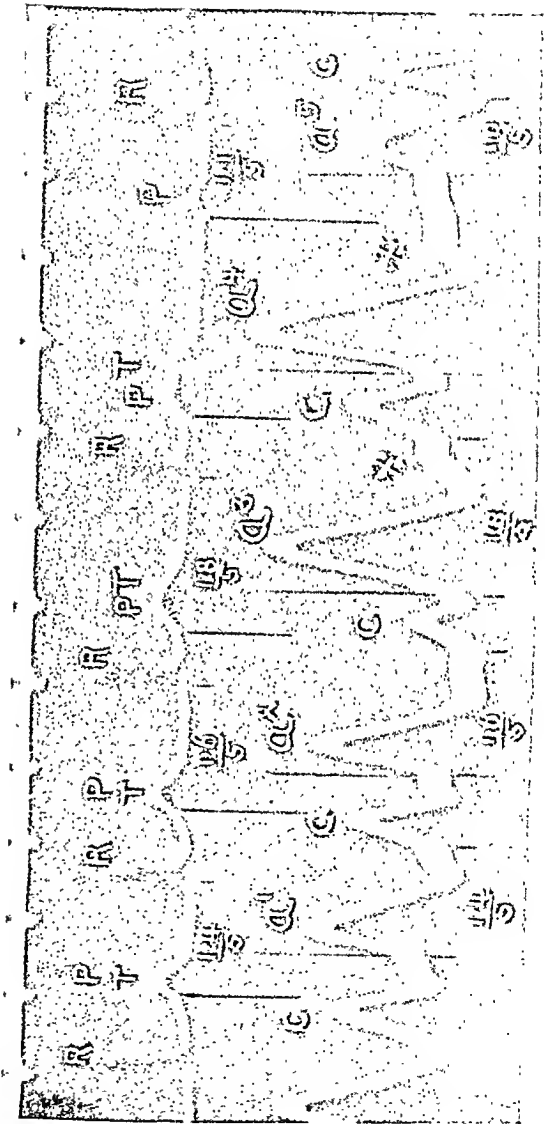


FIG. 13



# A STUDY OF THE ALTERATIONS OF THE HYDROCHLORIC ACID IN THE GASTRIC JUICE, DUE TO CARCINOMA OF THE STOMACH

By GEORGE GRAHAM

SINCE the original discovery by von den Velden (21) in 1879, that free hydrochloric acid was not present in the stomach when dilatation was caused by carcinoma of the pylorus, a great many papers have been written on this subject. It is not necessary to deal here with the work of the first twenty years, as full accounts of it have been published by many of the authors quoted in this paper. In spite of all the work which has been done, neither the cause of the absence of hydrochloric acid nor the frequency with which this change takes place has yet been settled.

Reissner (15 and 16) in 1901 showed that the hydrochloric acid was much diminished and the mineral chlorides were increased in nearly every case of carcinoma of the stomach. He thought that the diminution of the acid could be explained by neutralization with an alkali. Emerson (6) in 1902 also concluded, on different grounds, that neutralization of the acid took place. That a diminution of the active acid is accompanied by an increase in the amount of mineral chlorides was further confirmed by Clowes and Jeffcott (2) in 1904. Von Tabora (20) in 1904 thought the change was due to two causes:— (1) A neutralization which took place when the pylorus was affected; (2) a chronic gastritis which occurred when the growth was on the lesser curvature of the stomach. Willcox (23, 24, 25, 26) in 1905 found that the acid was diminished in all the cases of malignant disease which he had examined. He did not notice any increase in the mineral chlorides. Moore (11, 12, 13) in 1905 advanced the hypothesis that the absence of hydrochloric acid was not due to a local condition in the stomach, but to general conditions set up in the body by the new growth, which need not necessarily be in the stomach. Copeman and Hake (3, 4) have been unable to confirm Moore's work. I have made various experiments to test the accuracy of the methods employed, and have collected a series of cases in which a routine examination has been made.

## I. *Methods.*

The test meal which I have employed throughout my series of cases consists of a pint of weak tea without milk or sugar and two pieces of toast, about 2 oz. It is usually given at 9.0 a.m., after the patient has fasted since



midnight or, which is better, has just had his stomach washed out with water. About one hour afterwards, the contents of the stomach are siphoned off by means of the stomach tube without the addition of water. No water is added because it reduces the value of the chemical analysis for comparative results. If the food does not at once appear in the tube, the patient is instructed to take a few long deep breaths; this will sometimes start the flow, and the siphon action will then empty the stomach. If this is not effective, the flow up the tube should be started by creating a slight vacuum. I have found Senoran's stomach aspirator (made by Allen and Hanbury) very useful for this purpose, and as a large vacuum cannot be created, little danger of damage to the gastric mucous membrane exists. Occasionally nothing at all can be withdrawn, and the stomach should then be washed out with water to ascertain that there is nothing left in it.

The volume of the gastric contents should be measured, and is of some importance, since it affords evidence of the motor power of the stomach. Sometimes nearly the whole pint can be recovered, while at others only an ounce or two. The reaction of the gastric contents is nearly always acid, and the acidity should be estimated quantitatively by titrating 10 c.c. of the filtered gastric contents with an  $\frac{N}{10}$  soda solution, using phenolphthaleïn as an indicator.

The results obtained are accurate, but owing to the yellowish colour of the fluid the precise end-point is sometimes difficult to observe. The results are best expressed by the number of grammes of hydrochloric acid in 100 c.c. of the gastric contents, assuming that the total acidity is due to the hydrochloric acid.

The fact that the gastric contents are acid in reaction has long been known, but it was not until 1824 that Prout (14) showed that the acid present was hydrochloric acid, or muriatic acid as it was named at that time. This observation was at first disbelieved, and it was not until 1852 that Bidder and Schmidt (1) conclusively proved the acid to be hydrochloric acid. Since then the fact has been established by other workers. In 1872 Richet (17), who made several fresh observations on the gastric juice, came to the conclusion that hydrochloric acid was the only acid present, and that it did not exist in the free state but was loosely combined with some organic matter.

The total acidity of the pure gastric juice is not due to the hydrochloric acid alone, because acid phosphates are also present. Still less does the total acidity of the gastric contents represent the hydrochloric acid, for in addition to the acid salts, lactic and butyric acids may be present.

A great many methods of detecting the free hydrochloric acid have been devised, but only two are accurate.

The Günsberg reagent (Willcox modification) contains phloroglucin 4 grains, vanillin 2 grains, dissolved in 1 c.c. of absolute alcohol. This solution must be freshly made up, as it does not keep well. Two c.c. of filtered gastric contents are mixed with it in an evaporating basin and heated to dryness over a water-bath. A bright red colour indicates the presence of free hydro-

chloric acid. Willcox has been able to detect it even in a dilution of 1 in 100,000. The test is not disturbed by the presence of lactic acid, other organic acids, or by salts of hydrochloric acid.

The Boas reagent contains cane sugar, grm. v; resorcin, grm. iii; water, 50 c.c.; methylated spirit, 50 c.c. This reagent acts in a similar way, and is nearly as delicate as the Günsberg. It keeps its properties better and is also much cheaper.

These two reagents form definite coloured condensation products with the hydrochloric acid and are direct tests for its presence. Several other reagents have been used for detecting free hydrochloric acid, e.g. Congo red; tropaeolin O O; alizarin; dimethylamidoazobenzene. These indicators are all reagents for detecting the H ions, and any substance which has a sufficient concentration of H ions will react with them. They are not all equally sensitive, and the results obtained on titrating a complex fluid like the gastric contents with an  $\frac{N}{10}$  soda solution vary with the indicator used. Consequently a search has

been made for an indicator which is only affected by free hydrochloric acid. Dimethylamidoazobenzene has been called the indicator for free hydrochloric acid. However, it only measures the number of H ions present in the solution, and if lactic acid or organic salts of hydrochloric acid are present in sufficient concentration they will increase the titration figures for the free hydrochloric acid. Willcox (23) has been able to detect lactic acid in a dilution of 1 in 10,000 with the dimethyl indicator. I have mixed the amido-acid glycocoll with  $\frac{N}{10}$  hydrochloric acid in such proportions that no hydrochloric acid was left uncombined, and this was confirmed by using the Günsberg reagent and the Prout Winter method. But the dimethyl indicator gave a crimson colour showing the presence of H ions. Hence the dimethyl indicator cannot be accepted as an accurate test for free hydrochloric acid, for if the H ions of organic acids and hydrolysable salts of hydrochloric acid are in sufficient concentration the indicator is affected. The same argument holds good for the other indicators of this class, and they react to H ions in a less concentration than the dimethyl indicator. But the qualitative tests for the presence or absence of free hydrochloric acid are of little value as an aid to diagnosis, and quantitative estimations must be made. A great many methods of estimating the free hydrochloric acid have been devised. They may be divided into three classes, viz.:—(1) Simple titration methods with different indicators. (2) Estimation of the chlorides. (3) Experiments which depend on the free mineral acid producing an easily estimated change in another substance.

I. *Toepfer's method.* This consists in titrating 10 c.c. of the filtered gastric contents with  $\frac{N}{10}$  soda, using several indicators. Thus the total acidity is determined by means of phenolphthaleïn; the free acids by means of alizarin; the free hydrochloric acid by dimethylamidoazobenzene, which was thought

to be unaffected by organic acids or acid salts. I have already discussed the principle of this method and shown that the results obtained by it cannot be at all accurate. A modification of the method consists in using Günsberg or Boas reagents for estimating the free hydrochloric acid. This method is an accurate one, but it is exceedingly tedious to carry out, as the evaporation of the reagent on the water-bath takes some time and must be repeated at frequent intervals.

I have estimated the free hydrochloric acid by Winter and Hayem's modification of the original method by which Prout (14) demonstrated the presence of this acid in the gastric juice.

II. *Prout Winter method.* A. 10 c.c. of the filtered gastric contents are mixed with excess of sodium bicarbonate in a platinum crucible and evaporated to dryness over a water-bath. The contents of the crucible are then heated over a Bunsen flame and incinerated, thus driving off all the organic matter but retaining all the chlorine as a mineral chloride. The ash is then extracted with hot water and filtered: the chlorides in the solution are estimated by Volhard's sulphocyanide method. The total amount of chlorine originally present in the gastric juice is estimated by this experiment, and is expressed in terms of hydrochloric acid per 100 c.c.

B. This experiment is then repeated, but the sodium bicarbonate is not added until the solution has been evaporated to dryness, thus distilling off the free hydrochloric acid. The chlorine combined with organic and inorganic matter is determined by this experiment. The amount of free hydrochloric acid originally present is estimated by subtracting the result of Experiment B from that of Experiment A.

C. Finally the experiment is repeated without any additions, and the chlorine in combination with a mineral base is determined. The quantity of chlorine combined with organic matter is obtained by subtracting the result of Experiment C from that of Experiment B, and this figure represents the protein hydrochloric acid. By subtracting the result of Experiment C from that of Experiment A the 'physiologically active' hydrochloric acid is determined. This method, which has been extensively used by Winter and Hayem and also by Verhaegen (26), is easy to use, and although the experiment takes some hours to complete, it requires little attention until the last hour.

Willcox (25) has used a modification of the Prout Winter method. Only Experiments A and C are performed and the 'active' acid is estimated. Willcox does not think that it is necessary to filter the black ash from the solution, but I prefer to filter as the end-point of the titration is thereby made much easier. Willcox has found that this method gives accurate results and my controls for Experiments A and C also show close agreement. But the controls for Experiment B, where the free hydrochloric acid is distilled away, do not agree so well together as the others do.

Verhaegen considered that if the fluid was very viscid all the free acid might not be driven off, but on experimenting with a 10 per cent. solution

of glucose and adding distilled water at least once before finally evaporating to dryness, he found that practically no free acid was left behind in the ash. Hence if the gastric contents are very viscid, they should be diluted with distilled water at least once before the final evaporation to dryness.

Willcox (24) repeated the experiment with a solution of dextrose, but found that he was unable to distil off more than 33 per cent. of the free hydrochloric acid. I have repeated the experiment, using Verhaegen's precautions, with glucose solutions of various strengths. These experiments show that with solutions containing 5 per cent. of glucose, 78 per cent. of the free hydrochloric acid can be distilled away. With 7.5 and 10 per cent. glucose solutions only 33 per cent. of the free acid can be distilled away. The 7.5 and 10 per cent. glucose solutions are much more viscid than the gastric contents usually are, and cannot be evaporated to dryness. Therefore when the gastric contents are very viscid, all the free acid will not be distilled away and the results will be much too low. However, the gastric contents are most viscid when no free hydrochloric acid is present and when the digestion of the proteins of the food has not proceeded far. Hence in the majority of the cases the results will only be a little too low, and they afford some useful information about the composition of the 'active' acid.

Reissner (16) has introduced another modification of this method. He neutralizes 10 c.c. of the gastric contents, using litmus as an indicator, and then treats the solution in the usual manner. By this method he distils away the volatile salts of hydrochloric acid which are not neutralized when litmus changes colour. The correct figure for the 'active' HCl is obtained by subtracting the results of Experiment C from this one.

III. The katalysis of methyl acetate has been used by Moore, in conjunction with Alexander, Roaf, and Kelly (12), to estimate the free hydrochloric acid. This method depends on the law that the rate of the hydrolysis of methyl acetate is accelerated by the presence of H ions. Hence it measures the concentration of the H ions and not the quantity of hydrochloric acid present. But hydrochloric acid is a much stronger acid than the organic acids, lactic and butyric acid, which may be present in the gastric contents, as Ostwald's figures show :

Hydrochloric acid . . . . .	= 1.0
Lactic acid . . . . .	= 0.00901
Butyric acid . . . . .	= 0.00299

Consequently the presence of small quantities of the organic acids will not affect the rate of the hydrolysis to any extent. The free hydrochloric acid can be estimated accurately by this method, but if any of the acid has combined with protein to form a salt, a large error will at once occur. The salts of hydrochloric acid are much less readily ionized than the free acid, and cannot accelerate the hydrolysis of methyl acetate so much as the free acid does. Hence the results obtained will be much too low.

I have tested the accuracy of the methyl acetate method by using a mixture of protein and hydrochloric acid of known strength :—

A. With a solution of Witte's peptone 0.45 grm. + 0.292 grm. of hydrochloric acid in 100 c.c.

Prout Winter Method.			Methyl Acetate Method.
Free HCl	0.238 grm.	. . . . .	0.256 grm. per 100 c.c.
Combined HCl	0.054 "		
Total HCl	0.292 "		∴ Error = 0.036.

The Prout Winter figures for the free HCl are a little lower than those of the methyl acetate method. This may be due either to the incomplete distillation of the free acid or to partial action of the peptone combination in hastening the hydrolysis of the methyl acetate.

B. With a solution of glycocoll 0.292 grm. + 0.304 grm. of hydrochloric acid in 100 c.c.

By Calculation.			By Methyl Acetate Method.
Free HCl	0.162 grm.	. . . . .	0.160 grm. per 100 c.c.
Combined HCl.	0.142 "		
Total HCl	0.304 "		∴ Error = 0.144.

These experiments show that the hydrochloric acid has combined with some of the peptone and glycocoll and can no longer hasten the hydrolysis of the methyl acetate.

But the proteins of the bread given in the test meal are broken down by the digestive action of the stomach into albumoses, peptones, and polypeptides. The peptone, as I have shown, is capable of combining with hydrochloric acid and of rendering it inactive to methyl acetate. I have not been able to experiment with a polypeptide, which is a chain of amido-acids, but only with the pure amido-acid glycocoll which combined with a great deal of hydrochloric acid; this combination was inactive with methyl acetate.

Hence when the protein of the food is broken down during digestion, some of the hydrochloric acid will combine with some of the broken-down products, and will no longer be detected by the methyl acetate method, although of course it will still be estimated by the Prout Winter method.

Copeman and Hake (3) employed both methods to estimate the hydrochloric acid occurring in test meals. They found that the methyl acetate method gave much lower figures for the hydrochloric acid than the Prout Winter method did.

We may therefore conclude that the methyl acetate method is only capable of estimating the amount of hydrochloric acid which is actually in the free state or very feebly combined, and takes no account at all of acid which was originally free and has now combined with the food. Consequently the methyl acetate method is not of great value in gastric analysis, while the Prout Winter method, which takes account of hydrochloric acid already used up, is a much more valuable method.

Opinions unfortunately differ as to the part played in digestion by the acid when combined with proteins. Moore (13) considers that hydrochloric acid, which is so firmly united with organic matter that it cannot hasten the velocity of the methyl acetate hydrolysis, is physiologically inactive and therefore cannot be of use in aiding digestion. He admits that this hydrochloric acid is combined with some organic matter, but he is unaware of its nature. He tried to estimate the ammonia present by Schlossing's method, but was unable to obtain more than a trace. Willcox, following Lüttke (10), classes together the free hydrochloric acid and the acid present in combination with protein and calls the sum of these two the active hydrochloric acid, for he considers that both kinds of acid play an important part in digestion.

Dresler (5) has made some experiments with hydrochloric acid and glycocoll, which combine together to form a salt. He has found that the digestive power of a solution of hydrochloric acid and pepsin is not impaired by the addition of glycocoll in sufficient quantities to combine with all the free hydrochloric acid. This combination, as I have already shown, does not give the tests for free hydrochloric acid; however, these experiments show that it is still available for aiding digestive action. Hence the estimation of the amount of active acid is of great importance.

With regard to Moore's suggestion that some of the 'active' acid is really present as an ammonium salt, I have made a few determinations of the amount of ammonia present in the gastric content, using Shaffer's method (19), which is much more delicate and reliable than Schlossing's method, which Moore used.

	Quantity of $\text{NH}_3$ present in grm. per 100 c.c.	Quantity of HCl neutralized in grm. per 100 c.c.	Quantity of active HCl in grm. per 100 c.c. Prout Winter Method.
I. Gastric ulcer . . .	0.0047	0.0109	0.296
II. Dilated stomach . .	0.00263	0.0056	0.148
III. Carcinoma of pylorus	0.0055	0.0118	0.0092

These experiments show that in Cases 1 and 2 the amount of hydrochloric acid neutralized by ammonia and present as a 'fixed' salt is very small compared with the amount of 'active' acid. In Case 3, where carcinoma of the pylorus existed, the figures for the 'active' acid are very low and more than sufficient ammonia was found to neutralize all the active acid. Hence, in this experiment the term 'active' acid is a misnomer.

The total mineral chlorides contained in 2 oz. of toast are equivalent to 0.22 grm. of hydrochloric acid. This quantity of mineral chlorides is given in 20 oz. or 600 c.c. of weak tea which contain practically no mineral chlorides. Very little absorption of fluid takes place in the stomach, and the stomach contents are usually discharged into the duodenum practically unaltered in volume. Hence 100 c.c. of gastric contents will contain 0.036 grm. of mineral chlorides calculated as HCl. Consequently, the figures for the total and mineral chlorides are 0.036 grm. too high.

*Lactic acid.* The usual tests for this acid are not reliable and are practically

worthless unless the lactic acid is first extracted from the gastric contents by ether. In Uffelman's test, one drop of ferric chloride is mixed with 2 per cent. phenol, giving a clear amethyst-blue coloured solution. Lactic acid turns the colour yellow while hydrochloric acid only discolours it.

Hopkins's (7) test is reliable but requires a good deal of time, because the lactic acid must be carefully extracted, or else the gastric contents char with the sulphuric acid and obscure the colour reactions.

## II. *Details of Analyses.*

One of the chief difficulties in pursuing these researches is that of ascertaining exactly from what disease the patient is suffering. Many patients, if they improve in health, leave the hospital and are lost sight of, while if they die outside the hospital, it is almost impossible to obtain an autopsy. Even the cases which are operated on in hospital present some difficulties: an advanced carcinoma of the stomach is easy to diagnose, but the majority of cases are difficult. I have seen two cases of ulcerated stomach in the autopsy room where the parts can be easily handled and the stomach opened affording a good view, when expert opinion has differed as to whether the ulcer was innocent or malignant. The absence of metastatic deposits pointed to innocence, and this on microscopical examination was confirmed. It is therefore not surprising that an error in diagnosis is occasionally made during a laparotomy, when the stomach can only be felt, or seen, from the outside.

Cases 56 and 57 in my series exemplify this difficulty. From an examination of the test meal in Case 56, I decided that the patient had certainly not got malignant disease. The surgeon who performed the operation found a hard mass on the lesser curvature of the stomach, some hard glands in the lesser omentum, and felt some secondary nodules on the liver; and consequently attempted nothing further. This patient is still alive, although two years have elapsed since the operation. He has become slightly thinner, but otherwise his condition has altered very little. The after history of this case renders it very improbable that the mass felt in the lesser curvature was a malignant growth; the glands were probably inflammatory in nature. I cannot explain in any way the nodules felt on the liver.

Case 57 was considered at the operation to have a malignant ulcer of the stomach and secondary deposits in the retroperitoneal glands; the autopsy showed a chronic ulcer on the lesser curvature of the stomach which microscopically only showed inflammatory changes; the glands adherent to the stomach also showed inflammatory changes; the lumbar and bronchial glands showed a widespread dissemination of a spheroidal-celled carcinoma; a nodule in the kidney, as big as a hazel nut, also showed a spheroidal-celled carcinoma. The primary source of this carcinoma is not quite clear, but it is certainly not in the stomach. This agrees with the result of the test meal, which is typical of a gastric ulcer.

For the purpose of comparison with the malignant cases, I have given the

figures for some of the innocent cases which I have examined. I have always estimated the quantities of free hydrochloric acid, active hydrochloric acid and mineral chlorides present in the gastric contents, and in another column I have set out the ratio between the active hydrochloric acid and the mineral chlorides, which ratio I find of assistance in making a diagnosis.

TABLE I

Determination by the Prout Winter Method. HCl reckoned  
in grammes per 100 c.c. of gastric contents.

No.	Age.	Diagnosis.	Quantity recovered.	Total acidity in grammes of HCl per 100 c.c.	Free HCl.	'Active' HCl composed of free HCl and protein HCl.	Mineral salts of HCl reckoned as HCl.	Ratio of active HCl to mineral salts of HCl.	Total chlorides.	Lactic acid.
1	35 circa	Gastric ulcer. Operation. Gastro-entero- stomy.	—	—	trace	0.153	0.044	347:100	0.197	—
2	40	Duodenal ulcer. Operation. Gastro-entero- stomy.	—	0.365	0.062	0.301	0.155	193:100	0.456	0
3	56	Died after a per- foration. P.M. Duodenal ulcer.	—	—	0.029	0.229	0.083	275:100	0.312	—
4	39	P.M. Duodenal ulcer, adherent to everything near. Section, inflam- matory.	—	—	0.044	0.294	0.090	327:100	0.384	—
5	53	P.M. Gastric ulcer, adherent to everything near. Section, inflammatory.	—	—	0.029	0.237	0.098	241:100	0.335	—
6	33	Gastric ulcer. Operation. Gastro-entero- stomy.	—	—	0.058	0.209	0.105	200:100	0.314	—
7	40	Ulcer on lesser curvature of stomach. Opera- tion. Section, in- flammatory.	—	—	0.030	0.215	0.201	107:100	0.416	0
8	39	Old gastric ulcer.	—	—	0.025	0.248	0.080	310:100	0.328	0
9	48	? Duodenal ulcer.	—	0.225	0.040	0.174	0.119	146:100	0.293	0
10	49	Severe haema- temesis and melaena.	180 c.c.	—	0.080	0.410	0.090	455:100	0.500	0
11	48	Duodenal ulcer. Operation. Severe melaena.	160 c.c.	—	0	0.134	0.116	115:100	0.250	—

NOTES.—2. The mineral chlorides are much increased. ? Regurgitation of alkaline fluid from duodenum.  
5. Blood in test meal. 7. The mineral chlorides are much increased. ? Regurgitation of alkaline fluid from  
duodenum. 9. Occult blood in faeces. 10. Removed after 2 hours. 11. Test meal when very anaemic.



TABLE I (*continued*)

No.	Age.	Diagnosis.	Quantity recovered.	Total acidity in grammes of HCl per 100 c.c.	Free HCl.	'Active' HCl composed of free HCl and protein HCl.	Mineral salts of HCl reckoned as HCl.	Ratio of active HCl to mineral salts of HCl.	Total chlorides.	Lactic acid.
12		Vomiting. ? Ulcer.	—	0.335	0.040	0.285	0.116	245 : 100	0.401	—
13	39	? Ulcer.	250 c.c.		0.105	0.291	0.077	377 : 100	0.368	—
14	23	Hyperchlorhydria. Operation. Nil found.	—	0.325	0.051	0.346	0.076	455 : 100	0.422	—
15	50	Hyperchlorhydria.	180 c.c.	—	0.140	0.365	0.065	561 : 100	0.430	—
16	—	? Hyperchlorhydria. ? Ulcer.	420 c.c.	0.219	0.050	0.225	0.085	264 : 100	0.310	—
17	35	Pyloric obstruction. Operation. Scar of ulcer. Gastro-enterostomy. Quite well 2 years after.	—	0.175	0.086	0.182	0.094	193 : 100	0.276	0
18	43	Dilated stomach. Improved.	—	0.273	0.024	0.164	0.102	160 : 100	0.266	+
19	53	Pyloric obstruction. Operation. Scar tissue at pylorus and omental adhesion. Gastro-enterostomy.	—	—	trace	0.127	0.117	108 : 100	0.244	—
20	48	Pyloric obstruction. Scar of old ulcer. Gastro-enterostomy.	250 c.c.	—	trace	0.148	0.100	148 : 100	0.248	—
Average					0.04	0.236	0.099	236 : 100	0.335	

NOTE.—18. Removed after half an hour.

The general characteristics of the cases shown in this table are:—

- (1) The presence of a fair amount of free hydrochloric acid.
- (2) The presence of a good deal of active hydrochloric acid.
- (3) The presence of mineral chlorides in small quantities.
- (4) The high ratio between the active acid and the mineral chlorides.

All the cases conform to the same general type except Case 11, which had recently had a great deal of melaena and was very anaemic. An examination of the figures fails to show any marked difference between the cases of ulcer and uncomplicated hyperchlorhydria. In both these conditions the acid secretion is high, and this differentiates them from the other groups of cases. But the differential diagnosis must be made by a careful consideration of the history,

physical signs, and progress of the case. The cases of dilated stomach, due to scars or adhesion, all show a fairly high active acid to mineral chloride ratio and form a striking contrast to those due to carcinoma of the pylorus.

TABLE II

Determination by the Prout Winter Method. HCl reckoned  
in grammes per 100 c.c. of gastric contents.

No.	Age.	Diagnosis.	Quantity recovered.	Total acidity in grammes of HCl per 100 c.c.	Free HCl.	'Active' HCl composed of free HCl and protein HCl.	Mineral salts of HCl reckoned as HCl	Ratio of active HCl to mineral salts of HCl.	Total chlorides.	Lactic acid.
21	24	Dyspepsia. Improved on Salisbury diet.	240 c.c.	0.156	0.009	0.150	0.082	182 : 100	0.232	0
22	24	Dyspepsia.	180 c.c.	—	0.022	0.171	0.124	137 : 100	0.295	0
23	—	Dyspepsia.	—	—	0	0.197	0.135	145 : 100	0.332	—
24	50 circa	Dyspepsia and Mucous colitis.	—	0.175	0.033	0.170	0.065	261 : 100	0.235	0
			Large dose of NaHCO <sub>3</sub> taken in night.	Alkaline	0	0	0.242	0 : 100	0.242	0
25	62	Dyspepsia.	—	—	0	0.113	0.054	209 : 100	0.167	—
26	52	Dyspepsia.	160 c.c. circa	—	0.0037	0.202	0.104	194 : 100	0.306	0
27	28	Dyspepsia.	Water added	—	0.02	0.137	0.091	150 : 100	0.228	—
Average excluding 24 (ii) and 27						0.182	0.094	193 : 100	0.256	

NOTES.—22 and 23. Mineral chlorides increased. ? Regurgitation from duodenum. 24 (i). Gastric lavage before test meal.

The general characteristics of this class are :—

- (1) The diminution of the free hydrochloric acid.
- (2) The presence of a fair quantity of active hydrochloric acid.
- (3) The presence of mineral chlorides in small quantity,
- (4) The comparatively high ratio between the active acid and mineral chloride, this never declining below 137 : 100.

All the patients tested had chronic dyspepsia which was of some years' standing, and all improved on treatment. The gastric analysis is of importance as it practically excludes both gastric ulcer and malignant disease.

TABLE III

Determination by the Prout Winter Method. HCl reckoned  
in grammes per 100 c.c. of gastric contents.

No.	Age.	Diagnosis.	Quantity recovered.	Total acidity in grammes of HCl per 100 c.c.	Free HCl.	'Active' HCl composed of free HCl and protein HCl.	Mineral salts of HCl reckoned as HCl.	Ratio of active HCl to mineral salts of HCl.	Total chlorides.	Lactic acid.
28	56	Carcinoma of pylorus. Large secondary mass in liver. Died 3 months later.	180 c.c.	—	trace	0.175	0.219	80:100	0.394	+
29	65	Carcinoma of stomach. Died 4 months later.	150 c.c.	—	0.037	0.135	0.146	92.4:100	0.281	—
30	43	Carcinoma of pylorus. Ascites. Died 1 month later.	—	—	0	0.139	0.196	70:100	0.335	—
31	70	Carcinoma of pylorus. Lump felt. Died 4 months later.	—	—	0	0.074	0.133	55.6:100	0.207	—
32	48	Spheroidal-celled carcinoma of pylorus. Operation.	150 c.c. 170 c.c.	0.127 0.13	0 0	0.107 0.080	0.151 0.164	71:100 50:100	0.258 0.244	— —
33	62	? Carcinoma of stomach. Died 9 months later.	90 c.c. 180 c.c.	— —	0 0	0.069 0.014	0.084 0.109	82:100 13:100	0.153 0.123	— —
34	59	P.M. Spheroidal-celled carcinoma of pylorus.	330 c.c.	0.2	0	0.052	0.171	30.5:100	0.225	0
35	44	Carcinoma of stomach. Secondary mass in liver.	450 c.c.	—	0	0.051	0.200	25:100	0.251	+
36	38	Carcinoma of stomach. Operation.	—	—	0.005	0.045	0.186	24:100	0.231	—
37	61	Carcinoma of pylorus. Died 6 months later.	—	—	0	0.040	0.146	27:100	0.186	—
38	59	P.M. Carcinoma of oesophagus and stomach. Metastases in liver, spleen, and pancreas.	—	—	0	0.015	0.156	10:100	0.171	—
39	50	Carcinoma of stomach. Operation.	—	—	0.007	0.015	0.145	10:100	0.160	—
40	39	Carcinoma of pylorus. Operation. Died 3 months later.	—	—	0	0.013	0.206	6.3:100	0.219	—

NOTES.—28. Blood in test meal. 32 (i). Oppler Boas bacillus. 32 (ii). Oppler Boas bacillus.  
34. Oppler Boas bacillus. 35. Oppler Boas bacillus.

TABLE III (*continued*)

No.	Age.	Diagnosis.	Quantity recovered.	Total acidity in grammes of HCl per 100 c.c.	Free HCl.	'Active' HCl composed of free HCl and protein HCl.	Mineral salts of HCl reckoned as HCl.	Ratio of active HCl to mineral salts of HCl.	Total chlorides.	Lactic acid.
41	42	Carcinoma of stomach and duodenum. Operation.	—	—	0	0.014	0.101	13.8:100	0.115	+
42	58	Carcinoma of pylorus. Operation.	—	—	0	0.010	0.170	5.8:100	0.180	—
43	61	Carcinoma of stomach. Operation.	200 c.c.	—	0	0.018	0.131	13.7:100	0.149	—
44	57	Carcinoma of pylorus. Operation.	480 c.c.	—	0	0.009	0.129	7:100	0.138	—
45	—	Carcinoma of stomach. Operation.	—	—	0	0.007	0.175	4:100	0.182	—
46	52	Carcinoma of pylorus. Operation. Spheroidal-celled carcinoma.	—	—	0	0.003	0.082	3:100	0.085	—
47	50	Carcinoma of stomach. Operation.	—	—	0	0.036	0.044	82:100	0.080	—
48	42	Carcinoma of stomach. Operation.	—	—	0	0.018	0.079	23:100	0.097	—
49	42	Pylorus obstructed. Operation. Stomach wall very thick. ?Carcinoma. Piece of mucous membrane removed in gastro-enterostomy. Showed only inflammation.	—	0.16	0	0.040	0.058	70:100	0.098	0
Average						0.052	0.145	35.9:100	0.197	

NOTES.—43. Blood in test meal. 44. Oppler Boas bacillus. Anaerobic Gram + bacillus. 46. Oppler Boas bacillus. Water added to test meal.

The general characteristics of the cases shown in this table are :—

1. The diminution or complete absence of free hydrochloric acid.
2. The marked diminution of the active hydrochloric acid in nearly every case.
3. The presence of an absolute increase in the quantity of mineral chlorides in nearly every case.
4. The low ratio between the active acid and mineral chlorides, this ratio never exceeding 92.4:100.

Every case with these changes either has been proved to have malignant disease or is still under grave suspicion of having that disease.

I have found the comparison of the quantity of active acid with that of the mineral chlorides of great assistance in making a diagnosis. This relation is conveniently expressed as a ratio between the active acid and mineral chlorides, c. g. as  $x:100$ . Cases of gastric ulcer, hyperchlorhydria, dilation of the stomach due to scars or adhesion, all have a high ratio, e. g. 236:100. Cases of dyspepsia or chronic gastritis have a lower ratio, e. g. 193:100. But cases of carcinoma of the stomach all have a ratio of less than 93:100, and the ratio varies from this figure down to 10:100 or lower. Cases 28, 29, 30 in this series had over 0.13 grm. of active acid per 100 c.c., but as the mineral chlorides were higher than this figure, and as the ratio varied from 93:100 to 71:100, a diagnosis of carcinoma of the stomach was made. Unfortunately none of these three cases have been proved, by microscopical section, to have carcinoma, but the clinical picture and the rapid course of the disease make it almost certain that the diagnosis was correct.

Table IV contains eight cases; one of these has been proved to have a spheroidal-celled carcinoma of the pylorus; four patients are still thought to have carcinoma of the stomach; two patients were originally thought to have carcinoma, but their subsequent histories practically disprove this diagnosis; another patient who was thought to have carcinoma of the stomach at the operation has been proved by autopsy to have had a chronic inflammatory ulcer of the stomach, together with an infiltration of one kidney and many glands with a spheroidal-celled carcinoma. None of these cases show the usual clinical changes of carcinoma in their gastric contents. Hence one case, which has been proved to have carcinoma, out of twenty-three cannot be diagnosed by the gastric analysis, and if we accept the diagnosis of carcinoma in all the other four cases, five cases out of twenty-seven do not show the usual chemical changes.

Willcox has never seen a patient with plenty of active acid in the gastric contents who was proved to have carcinoma of the stomach. Several cases have been in dispute, but whenever an opportunity of settling the diagnosis has occurred, an innocent ulcer with an inflammatory thickening around it has been found. Reissner, who published eighteen cases of carcinoma of the stomach, records one case of proved and two of probable carcinoma where the gastric analysis was against that diagnosis.

These figures show that every case of carcinoma of the stomach does not have low active acid, high mineral chlorides, and a low ratio. Three of these cases, Nos. 50, 51, 52, while they have very high active acid, also have high mineral chlorides with ratios of 128, 150, and 110:100 respectively. The mineral chlorides here are particularly high and contrast strongly with the lowness of the mineral chlorides in the innocent cases and resemble the figures for the carcinoma cases. As I have already shown, three of the carcinoma cases, Nos. 28, 29, 30, have a good deal of active acid and would formerly have been diagnosed as innocent cases on this account.

TABLE IV

Determination by the Prout Winter Method. HCl reckoned  
in grammes per 100 c.c. of gastric contents.

No.	Age.	Diagnosis.	Quantity recovered.	Total acidity in grammes of HCl per 100 c.c.	Free HCl.	'Active' HCl composed of free HCl and protein HCl.	Mineral salts of HCl reckoned as HCl.	Ratio of active HCl to mineral salts of HCl.	Total chlorides.	Lactic acid.
50	39	Carcinoma of pylorus. Operation. Section, sphe-roidal-celled carcinoma.	—	0.219	0.033	0.195	0.152	128 : 100	0.347	0
51	—	Carcinoma of stomach. Operation. Has put on weight for 6 months. Now getting thinner again.	—	—	0.033	0.241	0.160	150 : 100	0.401	—
52	36	Carcinoma of pylorus. Operation. Glands along spine.	—	—	0.022	0.165	0.149	110 : 100	0.314	0
53	44	Operation. Stomach thickened throughout, especially at pylorus, where it was nodular. Wall oedematous throughout. Probably carcinoma.	—	—	0.112	0.285	0.123	231 : 100	0.408	—
54	56	Abdominal tumour. Alive and fat 1 year later.	—	—	0.01	0.08	0.04	200 : 100	0.12	—
55	55	Operation. Stomach thickened, and adherent to liver.	(1) — (2) —	— —	0.058 0	0.226 0.145	0.131 0.079	174 : 100 181 : 100	0.357 0.224	— —
56	40	Hard mass on lesser curvature. Glands in lesser omentum. Secondary nodules in liver. Still alive 2 years later. Condition unaltered.	160 c.c.	—	0	0.271	0.094	288 : 100	0.365	—
57	59	Autopsy. Ulcer of stomach. Section, inflammatory. Lymphatic glands adherent to stomach. Section, inflammatory. Nodule in one kidney. Bronchial and lumbar glands. Section, sphe-roidal-celled carcinoma.	—	—	0.021	0.205	0.069	300 : 100	0.274	—

NOTES.—51. Probably carcinoma. 54. Not carcinoma. 55. ? Carcinoma. 56. Innocent. Gastric. 57. Ulcer.

If the hypothesis which I shall discuss later on in this paper, that the diminution of the active acid is due to a neutralization by an alkali, be true, then the increase of the mineral chlorides may be the first sign that a carcinoma is growing in the stomach. If this is correct the increase of the mineral chlorides, if confirmed, in Case 50 and perhaps in Cases 51, 52, 53, would have been in favour of a diagnosis of carcinoma. Hence when the mineral chlorides are increased, if this is confirmed by a test meal repeated with special precautions, the diagnosis of carcinoma cannot be excluded. An exploratory laparotomy seems advisable in these cases, as the changes may be the signs either of an early carcinoma or of one which has not yet begun to ulcerate.

TABLE V

Determination by the Prout Winter Method. HCl reckoned  
in grammes per 100 c.c. of gastric contents.

No.	Age.	Diagnosis.	Quantity recovered.	Total acidity in grammes of HCl per 100 c.c.	Free HCl.	'Active' HCl composed of free HCl and protein HCl.	Mineral salts of HCl reckoned as HCl.	Ratio of active HCl to mineral salts of HCl.	Total chlorides.	Lactic acid.
58	30	? Gastric crisis.	—	—	0.110	0.252	0.131		0.383	—
59	32	Gastro-enterostomy 2 years before.	—	—	0.033	0.219	0.178	100:81	0.39	—
60	35	Operation. Scar at pylorus. Gastro-enterostomy. Improving.	—	—	0	0.037	0.233	100:740	0.270	—
61	56	Operation. Nothing abnormal.	—	—	0	0.110	0.197	100:179	0.303	—
62	20	Operation. Duodenal ulcer.	—	—	0	0.05	0.199	100:398	0.249	—
24		Gastritis.	—	Alkaline	0	0	0.242	—	0.242	—

NOTES.—58. Free iodine in gastric contents. Potassium iodide as medicine. 59. Probable regurgitation of alkalies through gastro-enterostomy opening. 60, 61, and 62. Mineral chlorides high. ?Regurgitation from duodenum. 24. Table II. Large dose of  $\text{NaHCO}_3$  taken in night before test meal.

Table V includes several cases where the active acid was low and the mineral chlorides were very high. In two cases no sign of carcinoma was observed at the time of operation. Reissner records three cases in which this also occurred. Clowes and Jeffcott also noticed this.

This condition may be accounted for in three ways:—(1) A dose of sodium bicarbonate may have been given by accident before the test meal was given. This would of course neutralize some of the acid. This actually occurred in Case 24, who was under my personal observation, and a second test meal, repeated with precautions, gave very different figures. In Case 58 the highness of the figures aroused suspicion, and, on testing, free iodine was found in the gastric contents. This patient was taking potassium iodide as a medicine, which accounts for the result obtained. (2) A regurgitation of the alkaline secretions

of the duodenum into the stomach may occur. If this has taken place, bile pigments will be present in the gastric contents. Reissner records one case in which he detected bile pigment. von Tabora states that in some cases of severe chronic gastritis or carcinoma of the lesser curvature which have been examined at operations, the pylorus has been found to be open. (3) In Reissner's three cases the filtration took several hours owing to the presence of a great deal of mucus, and he suggested that neutralization took place during this process.

These cases emphasize the importance of giving the test meal in a perfectly uniform way if any reliance is to be placed on the values for the mineral chlorides. The test meal should be repeated with special precautions against accidental error whenever the mineral chlorides are increased. I regret that this has not been done in most of the cases in this series, but I have only recently seen the great importance of this step.

### III. *Discussion of results.*

Four hypotheses have been suggested to account for the diminution of the hydrochloric acid: local ulceration, chronic gastritis, general condition (Moore), and neutralization.

1. *Local Ulceration.* If the cardiac end of the stomach is largely involved by carcinoma, the oxyntic cells will be affected or destroyed and will no longer be capable of secreting hydrochloric acid. But a growth at the pyloric end of the stomach causing obstruction and dilatation cannot directly affect the secretion of the oxyntic cells at the cardiac end of the stomach.

2. *Chronic Gastritis.* Rosenheim (18), who examined the stomachs of carcinoma cases after death, has found a marked atrophy of the mucous membrane with disappearance of its glands. This condition was most marked near the growth, but decreased in intensity as the distance from the growth increased. Hammerschlag has also found a severe gastritis around the new growths which have been removed by operation. This condition must cause a diminished secretion of gastric juice, but this change can only come on gradually. The increased amount of mineral chlorides which is usually found cannot be explained on this hypothesis. von Tabora, however, has found that in cases of carcinoma of the lesser curvature the gastritis is very well marked, and that in these cases the total chlorides are much decreased. Cases 47-49 in this series certainly show great diminution of the total chlorides, but the mineral chlorides are greater than the active acid. Hence a severe gastritis must be considered as the cause of the diminution of the acid in some cases.

3. *General Condition.* Moore has put forward the view that the diminution or absence of free hydrochloric acid in the gastric contents is not due to the local action of the malignant growth, but to a general condition set up in the body by the growth, and that carcinoma elsewhere in the body could produce the same effect. This view cannot be accepted for two reasons: first,



that the methyl acetate method used by Moore estimates the hydrochloric acid which is actually free, and, as I have shown, cannot estimate the amount of hydrochloric acid which has been secreted and is in active work in the stomach. Secondly, Copeman and Hake, who estimated the active acid by the Martius Lüttke method, in fourteen cases of carcinoma elsewhere in the body always found a large amount of active acid; although the free acid, as estimated by the methyl acetate method, was often low. They have come to the conclusion that a diagnosis of carcinoma elsewhere in the body cannot be made from the analysis of the gastric contents; and consequently the diminution of the active acid cannot be accounted for by general conditions set up by a carcinoma.

4. *Neutralization.* The increase of the mineral chlorides relative to the active acid is clearly shown by my series of cases, but the proof that it is an absolute increase is not so easy. A relative increase can be accounted for by a greater concentration of the gastric contents, which would give a higher figure for both the mineral chlorides and active acid. I have taken the following six cases from my series where the quantity had been measured.

*Innocent Cases.*

	Quantity removed.	Mineral salts of HCl	Ratio of active acid to mineral chlorides.
Case 10 . . .	180 c.c.	0.09 gramme per 100 c.c.	455:100
Case 15 . . .	180 "	0.06       "       "	561:100
Case 16 . . .	420 "	0.085     "       "	264:100

*Malignant Cases.*

Case 28 . . .	180 c.c.	0.219 gramme per 100 c.c.	80:100
Case 34 . . .	330 "	0.171     "       "	30.5:100
Case 35 . . .	450 "	0.20       "       "	25:100

These figures show that in an equal quantity of gastric contents recovered, the mineral chlorides in innocent cases are low and the active acid to mineral chloride ratio is greater than 100:100, in malignant cases the chlorides are two or three times as high and the ratio is less than 100:100.

They also show that the increase of the chlorides is an absolute one. The increase of the mineral chlorides may be caused in two ways:—by an increased secretion of the mineral salts in the gastric juice instead of free hydrochloric acid; or by the neutralization of the free acid by an alkaline fluid.

Schmidt's analysis of the pure gastric juice of a dog, whose salivary ducts had been ligatured, showed that mineral chlorides were secreted in it. Reissner (l.c.) has confirmed this statement.

There is no direct evidence against the hypothesis that mineral chlorides are secreted in increased quantities instead of free hydrochloric acid in cases of carcinoma of the stomach. But several experiments point to neutralization as being the more probable of the two causes. A comparison of the average amounts of active acid, mineral chlorides, and total chlorides in Tables I–III which are given in this paper throws some light on this point.

Averages.	Active HCl.	Mineral salts of HCl.	Total chlorides.
Table I . . .	0.236	0.099	0.335 gramme per 100 c.c.
Table II . . .	0.182	0.094	0.256   "   "
Table III . . .	0.052	0.145	0.197   "   "

This table shows that the average amount of active acid in Table I is 0.184 grm. higher than that in Table III, but the total chlorides in Table I are only 0.138 grm. higher than those in Table III. Also the average amount of active acid in Table II is 0.130 grm. higher than in Table III, while the total chlorides are only 0.059 grm. higher. Hence in carcinoma the total chlorides are decreased, but the active acid is much more decreased, while the mineral chlorides are increased. This condition may be explained by supposing that the acid secreted in the free state is neutralized at once by an alkaline fluid.

The results of the two test meals in Case 24 illustrate the change which may take place.

	Reaction.	Active HCl.	Mineral salts of HCl.	Total chlorides.
(i) Large dose of sodium bicarbonate taken in the night. Test meal at 9.0 a.m.	Alkaline	0	0.242	0.242
(ii) Stomach washed out before the test meal.	Acid } Free HCl }	0.170	0.065	0.235

In the first case the stomach contained an alkaline fluid which neutralized all the acid secreted for digestion. In the second case free and active acids were present and the mineral chlorides were low. The total chlorides secreted, after one hour, are almost identical in the two cases.

Willcox has examined several cases both before and after a gastroenterostomy had been performed. He found that the active hydrochloric acid, which had been present before the operation, was afterwards either absent or reduced in quantity. Case 59 in my series, which had had a gastroenterostomy performed two years before, had very high mineral chlorides besides plenty of active acid in the gastric contents. In these cases a regurgitation of the alkaline contents of the duodenum must take place and partially or wholly neutralize the free acid.

Honigmann and von Noorden (8) showed that the addition of free hydrochloric acid to the gastric contents of a carcinoma case liberated lactic acid. Honigmann (9) showed that the addition of hydrochloric acid to the gastric contents of a carcinoma patient caused an increase in the amount of mineral chlorides. These two experiments show that lactic acid or another weak organic acid must have been present as a salt.

Reissner (16) evaporated the gastric contents to dryness, incinerated and extracted the ash with water. The solution was either acid or neutral in innocent cases, but alkaline in many of the malignant ones. The alkalinity, he thinks, is caused by the presence of salts of organic acids in the gastric contents. These organic salts decompose on evaporation and incineration, forming sodium

carbonate and organic matter. The latter is vaporized, but the sodium carbonate is left behind in the ash and gives the alkaline reaction to the watery extract. This was confirmed independently by Emerson.

Lactic acid is not secreted by the stomach, but is formed by the action of micro-organisms (like the lactic acid bacillus) on carbohydrates, in the absence of hydrochloric acid. The acid produced will be in the free state. Hence if the lactic acid is present as a salt in the gastric contents it must have been neutralized by some alkali. These experiments all point to the probability of the presence of an alkaline fluid in the stomach of carcinoma cases. This alkaline fluid would have a greater avidity than the proteins of the food for the acid, and consequently very little acid will remain to aid digestion and check the growth of bacteria.

The alkaline fluid may come from various sources:—from alkalies in the medicine; this is avoided by careful methods. From regurgitation from the duodenum; this is impossible in cases of pyloric obstruction. From the mucus; this does not occur in the innocent cases. From blood present in the stomach; this is rarely present in sufficient quantity. And finally from an ulcer.

An innocent ulcer does not secrete alkalies, as in these cases a large amount of active acid is present but only a small quantity of mineral chlorides. The alkaline fluid may come from the malignant growth which has begun to ulcerate, and Reissner records one case where a tumour could be felt in the abdomen when the active acid was high and the mineral chlorides were low. While under observation, a complete inversion of this relation suddenly took place. This could be accounted for if the growth had begun to ulcerate and break down.

Reissner states that when the carcinoma is removed by operation, the hydrochloric acid is at once found in the gastric contents, thus showing that the alkaline fluid is no longer present to neutralize the acid. Emerson has tested the juice from a freshly removed carcinoma of the stomach and found that it was capable of neutralizing acids. Emerson has performed some experiments which suggest that the alkaline fluid is formed by an autolytic ferment which exists in the carcinoma.

### *Conclusions.*

1. Carcinoma of the stomach causes definite changes in the amount of active acid and mineral chlorides present in the gastric contents.
2. The increase in the mineral chlorides may be an earlier sign of carcinoma than the diminution of the active acid.
3. These changes can be observed in the great majority of cases.
4. This condition can be accounted for by the secretion of an alkaline fluid in the stomach, which neutralizes the acid.
5. The alkaline fluid is most probably secreted by a malignant growth which has begun to ulcerate.

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#### REFERENCES.

1. Bidder und Schmidt, *Die Verdauungssäfte und der Stoffwechsel*, Mitau u. Leipz., 1852, 46.
2. Clowes and Jeffcott, *Biochem. Centralbl.*, 1905, iii. 2073.
3. Copeman and Hake, *Proc. Roy. Soc.*, Lond., Ser. B, 1908, lxxx. 444.
4. Copeman and Hake, *Lancet*, Lond., 1909, i. 754.
5. Dreser, *Beitr. z. chem. Physiol. u. Path.*, Braunsch., 1906, viii. 285.
6. Emerson, *Deutsch. Arch. f. klin. Med.*, Leipz., 1902, lxxii. 415.
7. Fletcher and Hopkins, *Journ. Physiol.*, Camb., 1906-7, xxv. 308.
8. Honigmann und von Noorden, *Zeitschr. f. klin. Med.*, Berl., 1888, xiii. 88.
9. Honigmann, *Berl. klin. Woch.*, 1893, xxx. 351, 381.
10. Lüttke, *Deutsch. med. Woch.*, 1891, xxvii. 1325.
11. Moore, Alexander, Kelly, and Roaf, *Proc. Roy. Soc.*, Lond., Ser. B, 1905, lxxvi. 138.
12. Moore, Alexander, Kelly, and Roaf, *Biochem. Journ.*, Liverpool, 1906, i. 275.
13. Moore, *Biochem. Journ.*, Liverpool, 1908, iii. 449.
14. Prout, *Phil. Trans. Roy. Soc.*, Lond., 1824, cxiv. 45.
15. O. Reissner, *Verhandl. Cong. für innere Med.*, 1901, xix. 310.
16. O. Reissner, *Zeitschr. f. klin. Med.*, Berl., 1902, xlv. 71.
17. Richet, *Du Suc gastrique*, Paris, 1878, 24.
18. Rosenheim, *Deutsch. med. Woch.*, 1888, xxiv. 973.
19. Shaffer, *Amer. Jour. Physiol.*, 1903, viii. 330.
20. von Tabora, *Deutsch. med. Woch.*, 1905, xxxi. 578.
21. von den Velden, *Deutsch. Arch. für klin. Med.*, Leipz., 1879, xxiii. 369.
22. Verhaegen, *La Cellule*, 1897, xii. 33; xiii. 393.
23. Willcox, W. H., *Path. Trans.*, Lond., 1905, lvi. 250.
24. Willcox, W. H., *Lancet*, Lond., 1905, i. 1566; 1908, ii. 220.
25. Willcox, W. H., *Quart. Journ. Med.*, Oxford, 1909-10, iii. 93.
26. Willcox, W. H., *Lancet*, Lond., 1910, i. 1119.

# THE INFLUENCE OF SALICYLATES ON THE CARDIAC LESIONS OF CHOREA

By E. A. COCKAYNE

CHOREA appears to do no permanent harm to the brain, though by its long continuance or frequent recurrence it may seriously interfere with education. The movements produced by it may, however, throw a strain on a heart greatly weakened by coincident carditis, and it is in preventing this that the chief value of hypnotics lies.

From their efficacy in relieving the distressing joint pains and lowering the temperature in the acute attack of rheumatic fever, a belief has arisen that the salicylate compounds are a specific against the rheumatic organism, and that they have therefore the power of preventing the onset of carditis, or, if already present, of checking its further progress. If they have this action, they should be used in every case of chorea, either alone or in conjunction with some sedative. If they have no such influence, their use should be restricted to those cases in which there is some additional trouble, such as tonsilitis or arthritis, since in the doses usually given they have little or no action on the mental or motor phenomena of chorea.

At Dr. Garrod's suggestion I have recently examined the records of 780 cases of chorea, treated during the last eight years in the wards of the Hospital for Sick Children, Great Ormond Street, and have attempted to discover whether salicylates really have this power; and desire to thank the other members of the Staff for their kindness in permitting me to examine and use the records of cases under their care. Originally I intended to pick out those cases in which there was clinical evidence of the onset of endocarditis, myocarditis, or pericarditis whilst in the hospital, and to compare the number of such cases under treatment with salicylates with that of those under other treatment. The small number of the cases in which such an event definitely occurred compelled me to include those in which there was evidence of a fresh lighting-up of acute rheumatic processes in the heart. The cases chosen are strictly comparable in other respects, having been at rest in bed and under the same general treatment with regard to food and nursing.

For convenience I have divided them up into four groups. In the first (Table I) I have collected those cases in which there was no systolic murmur at the apex on admission to hospital, but in which one developed, either temporarily

or remaining still present on discharge from hospital. In some of these the murmur may have been present on admission, but remained undetected owing to the violence of the choreic movements. In others the heart may have been acting very feebly at first, and the murmur have developed without actual increase in the cardiac inflammation. The error due to these causes will have occurred equally in cases treated with or without salicylates, and so is unlikely to have vitiated the result.

A further subdivision has been made into cases in which the area of cardiac dullness (1) was decreased or not increased, (2) was not noted, or (3) was increased at the time of appearance of the murmur. In this group 22 cases are included, of which 14 were taking no salicylates, and 6 were under treatment with salicylates. It is difficult to say in how many the murmur was endocardial, but probably in most it was due to a temporary incompetence of the mitral orifice, caused by myocardial changes.

In the second group (Table II) are included the cases in which a mid-diastolic murmur appeared in addition to the apical systolic murmur, and in which neither a reduplicated second sound at the apex nor a mid-diastolic murmur had been heard within four days of admission to the hospital. The meaning of this triple sound limited to the apex is still rather obscure. The added sound may resemble the second sound, which appears to be reduplicated, or may be more commonly a definite murmur usually mid-diastolic in time, occasionally early diastolic or presystolic, but always soft and diminishing in intensity as it disappears, contrasting in these respects with the presystolic murmur of true mitral stenosis. Coombs (*Quarterly Journal of Medicine*, vol. ii, No. 5) is probably correct in considering it due to dilatation of the left ventricle caused by myocarditis, of which it may be an early sign, and he is supported by post-mortem observations. I have therefore considered all these cases as evidence of an increase of myocardial and not valvular inflammation. Of these cases there are 17, 8 treated without and 9 with salicylates.

My third group (Table IV) includes other cases of progressive myocarditis, in which the physical signs were more varied and are given in greater detail. In this group of 21 cases, 11 were treated with and 10 without salicylates. In the fourth group (Table V) are cases in which endocarditis appeared or progressed, or pericarditis supervened. It consists of 19 cases, 7 treated without and 12 with salicylates. In the last two tables additional columns show how long after treatment was the onset of fresh carditis, and any other rheumatic manifestation which appeared.

On adding together all the cases I obtain a total of 77, of which 39 were not treated, and 38 were treated with salicylates. Of the 780 cases, from which these were picked, 355 were given salicylates and 425 received other treatment: 156 cases received doses below 60 grs. a day, 95 between 60 and 100 grs., 60 between 100 and 200 grs., 19 between 200 and 300, and 8 doses of more than 300 grs. a day, and the remaining cases were treated with aspirin. If the drug has no effect the numbers showing cardiac change should be in the proportion of

39 untreated to 32 treated with salicylates, and the actual numbers obtained are so near these that the disparity can have no significance.

It might be thought that the larger doses would have had more effect in preventing the progress of the cardiac trouble, but the statistics do not suggest that the size of the dose has any such effect.

Lees states (*Brit. Med. Journ.*, 1909, i. 146) that very large doses, 300-400 grs. a day, have a most marked effect on the chorea and carditis, but too few cases were treated in this way for their effect to be shown in these statistics, and the remarks in this paper apply only to the more ordinary doses, up to 300 grs. a day. The salicylates were given in the form of sodium salicylate combined with about double the amount of sodium bicarbonate, except in the few cases where aspirin was administered.

To sum up my results: the organisms of rheumatism were probably present in the myocardium, endocardium, or pericardium in these cases, and the salicylates (in the doses usually given) appear to have had no action in preventing their entrance into the heart, nor in stopping their further activity when once established there. This is confirmed by their inability to check the continuance of that low intermittent fever, with its daily or almost daily rise usually to some point between 99 and 100° F., so characteristic of rheumatic infections in childhood.

The fact that they do not prevent the formation of subcutaneous nodules, and that they have no action on choreic movements, which is probably due to toxins elaborated by organisms lying near the blood-vessels of the cerebrum, and poisoning the nerve cells in their vicinity, would lead one to expect by analogy that they would have no action in the similar conditions found in the heart, and my results seem to show that this is the case.

TABLE I. *Systolic murmur localized to apex appeared.*

Cardiac Dullness.	No Salicylate.	Sod. Sal. under 60 grs. per diem.	Sod. Sal. 60- 100 grs. per diem.	Sod. Sal. over 100 grs. per diem.	Aspirin.
Not increased.	3	3			
Not noted.	7		1		
Increased.	4			1	1
Total .	14	3	1	1	1
	14		6		

TABLE II. *Mid-diastolic murmur developed in Ward.*

	No Salicylate.	Sod. Sal. under 60 grs. per diem.	Sod. Sal. 60- 100 grs. per diem.	Sod. Sal. over 100 grs. per diem.	Aspirin.
Total	8	3	3	2	1
	8		9		

TABLE III. *All Cases.*

	Dose under 60 grs. Sod. Sal. or Aspirin per diem.	Sod. Sal. 60-100 grs. per diem.	Sod. Sal. 100- 200 grs. per diem.	Sod. Sal. 200- 300 grs. and over per diem.
Total no. of Cases.	163	95	61	26
Cases developing cardiac change.	17	9	7	5
Percentage developing cardiac change.	10.4 %	9.4 %	11.4 %	19.2 %
Total developing cardiac changes (with no sod. sal.) 39 (9.4 %).				
" " " " (treated with sod. sal.) 38 (10.7 %).				

TABLE IV (*Myocarditis*).

Case 1. Age 7. Cardiac change: Mid-diastolic murmur developed; no systolic murmur present. Other manifestations: Erythema exudativum. Salicylates: none.

Case 2. Age 8. Cardiac change: Mid-diastolic murmur appeared with thrill; systolic murmur on admission. Other manifestations: Erythema marginatum; pyrexia 102° daily for 5 weeks. Salicylates: none.

Case 3. Age 10. Cardiac change: Systolic murmur localized to apex; area of cardiac dullness increased to R. and L. Time after treatment: 2 and 7 days. Other manifestations: Nodules; pyrexia. Salicylates: 30 grs. per diem.

Case 4. Age 8. Cardiac change: Temporary systolic murmur localized to apex with increase of cardiac dullness to R. and L.; dilatation increased even under doses of 100-150 grs. daily for 6 days, and 200-250 grs. for 5 days. Time after treatment: 4 days. Other manifestations: Pyrexia 99-99.4°, unaffected by 5 weeks' treatment with salicylates. Salicylates: 40 to 300 grs. per diem.

Case 5. Age 9. Cardiac change: Mid-diastolic murmur and area of cardiac dullness increased to R. and L. (natural on admission). Time after treatment: 6 days. Other manifestations: Pyrexia 99° and over almost daily. Salicylates: 90 grs. per diem.

Case 6. Age 5. Cardiac change: Mid-diastolic murmur with cantering rhythm and increased cardiac dilatation. Time after treatment: 4 days. Other manifestations: Nodules 13 days after treatment; pyrexia 99-99.6° daily. Salicylates: 30 grs. per diem.

Case 7. Age 8. Cardiac change: Mid-diastolic murmur appeared with increased dilatation to R.; death; P.M. myocarditis and endocarditis of mitral valve. Other manifestations: Pyrexia; extreme anaemia. Salicylates: none.

Case 8. Age 8. Cardiac change: Area of cardiac dullness increased to R. and L. Time after treatment: 28 days. Other manifestations: Nodules. Salicylates: none.

Case 9. Age 9. Cardiac change: Area of cardiac dullness increased to R. and L.; accentuated and reduplicated second sound at pulmonary base; no murmur. Time after treatment: 12 days. Salicylates: none.

Case 10. Age 6. Cardiac change: Mid-diastolic murmur developed; area of cardiac dullness not noted. Time after treatment: 10 days. Other manifestations: Nodules; erythema marginatum; pyrexia (intermittent) 100-101° daily, not affected by the salicylates. Salicylates: 120 grs. per diem.

Case 11. Age 8. Cardiac change: Area of cardiac dullness increased to R. and L.; cardiac irregularity. Time after treatment: 6 days. Other manifestations: Nodules; arthritis; pyrexia (intermittent) after 7 weeks of salicylate treatment. Salicylates: 40 to 80 grs. per diem.

Case 12. Age 4. Cardiac change: Cardiac dullness increased to L.; presystolic murmur altered to mid-diastolic. Other manifestations: Pyrexia 3 weeks. Salicylates: none.

Case 13. Age 8. Cardiac change: Cardiac dullness increased to R. and L. Time after treatment: 120 days. Other manifestations: Nodules. Salicylates: none.



39 untreated to 32 treated with salicylates, and the actual numbers obtained are so near these that the disparity can have no significance.

It might be thought that the larger doses would have had more effect in preventing the progress of the cardiac trouble, but the statistics do not suggest that the size of the dose has any such effect.

Lees states (*Brit. Med. Journ.*, 1909, i. 146) that very large doses, 300-400 grs. a day, have a most marked effect on the chorea and carditis, but too few cases were treated in this way for their effect to be shown in these statistics, and the remarks in this paper apply only to the more ordinary doses, up to 300 grs. a day. The salicylates were given in the form of sodium salicylate combined with about double the amount of sodium bicarbonate, except in the few cases where aspirin was administered.

To sum up my results: the organisms of rheumatism were probably present in the myocardium, endocardium, or pericardium in these cases, and the salicylates (in the doses usually given) appear to have had no action in preventing their entrance into the heart, nor in stopping their further activity when once established there. This is confirmed by their inability to check the continuance of that low intermittent fever, with its daily or almost daily rise usually to some point between 99 and 100° F., so characteristic of rheumatic infections in childhood.

The fact that they do not prevent the formation of subcutaneous nodules, and that they have no action on choreic movements, which is probably due to toxins elaborated by organisms lying near the blood-vessels of the cerebrum, and poisoning the nerve cells in their vicinity, would lead one to expect by analogy that they would have no action in the similar conditions found in the heart, and my results seem to show that this is the case.

TABLE I. *Systolic murmur localized to apex appeared.*

Cardiac Dullness.	No Salicylate.	Sod. Sal. under 60 grs. per diem.	Sod. Sal. 60-100 grs. per diem.	Sod. Sal. over 100 grs. per diem.	Aspirin.
Not increased.	3	3			
Not noted.	7		1		
Increased.	4			1	1
Total .	14	3	1	1	1
	14	6			

TABLE II. *Mid-diastolic murmur developed in Ward.*

	No Salicylate.	Sod. Sal. under 60 grs. per diem.	Sod. Sal. 60-100 grs. per diem.	Sod. Sal. over 100 grs. per diem.	Aspirin.
Total	8	3	3	2	1
	8	9			

Case 28. Cardiac change: Area of cardiac dullness increased to R. and L.; pericarditis; death. Time after treatment: 16 days. Other manifestations: Chorea developed with pericarditis. Salicylates: none.

Case 29. Age 9. Cardiac change: Pericarditis. Time after treatment: 11 days. Other manifestations: Erythema marginatum; nodules 20 days after beginning treatment. Salicylates: 120 to 300 grs. per diem.

Case 30. Age 8. Cardiac change: Area of cardiac dullness increased to R.; localized became conducted systolic murmur. Time after treatment: 18 days. Other manifestations: Intermittent fever. Salicylates: 20 grs. per diem.

Case 31. Age 10. Cardiac change: Area of cardiac dullness increased to R. and L.; presystolic murmur became mid-diastolic; pericarditis. Time after treatment: 6 days. Salicylates: 30 grs. per diem.

Case 32. Age 4. Cardiac change: Area of cardiac dullness (natural on admission) became increased to R. and L.; pericarditis. Time after treatment: 49 days. Salicylates: none.

Case 33. Age 7. Cardiac change: Area of cardiac dullness increased to R. and L.; alteration in character of systolic murmur; heart became more irregular; pericarditis and slight chorea 3 years later. Time after treatment: 49 days. Other manifestations: Nodules under first administration of sod. sal.; intermittent pyrexia throughout illness, except for two attacks of continued fever 3 and 12 weeks after beginning treatment. Salicylates: 120 grs. for 10 days, and 8 days later 120 to 180 grs. for 6 weeks.

Case 34. Age 11. Cardiac change: Area of cardiac dullness increased to R. and L.; occasional local systolic murmur became permanent and conducted. Time after treatment: 11 days. Other manifestations: Pyrexia; 97° to 99° or 100° almost daily. Salicylates: none.

Case 35. Age 8. Cardiac change: Area of cardiac dullness increased to L.; slightly conducted became better conducted systolic murmur; mid-diastolic murmur appeared. Time after treatment: 8 days. Other manifestations: Intermittent fever (99° F.) almost daily. Salicylates: 40.

Case 36. Age 7. Cardiac change: Conducted systolic murmur appeared at apex (no murmur on admission); cardiac dullness not noted. Time after treatment: 2 days. Salicylates: none.

Case 37. Age 10. Cardiac change: Cardiac dullness natural on admission; systolic murmur became harsher; mid-diastolic murmur developed; heart became irregular; cardiac dullness increased to R. and L., beginning 9th day and progressing up to 21st day after admission; pericarditis 6 months before treatment by sod. sal. 60 grs. daily for 14 days; T. 99° daily after this was stopped. Time after treatment: 9 days. Other manifestations: Intermittent fever 100.4-101° for first 14 days, then remaining high for 2 days; T. raised during and after treatment by salicylates. Salicylates: 90 grs. per diem, beginning 9th day. Aspirin: 15 grs. for first 5 days.

Case 38. Age 11. Cardiac change: Area of cardiac dullness increased; presystolic and mid-diastolic murmurs alternating; aortic systolic and diastolic murmurs developed. Other manifestations: Pyrexia. Salicylates: none.

Case 39. Age 11. Cardiac change: Increased cardiac dullness to R. and L.; presystolic murmur changed to mid-diastolic; aortic systolic and diastolic murmurs developed. Time after treatment: 17 days. Other manifestations: Nodules; continued fever for 17 days preceded and followed by intermittent fever. Salicylates: 30 to 60 grs. per diem.

Case 40. Age 8. Cardiac change: Cardiac dullness increased to R. and L. progressing during next 10 days; presystolic changed to mid-diastolic murmur; pericarditis. Time after treatment: 8 and 23 days. Other manifestations: Continued fever 9th-17th days, with intermittent pyrexia before and after. Salicylates: 40 grs. per diem, 4th to 15th day; 80, 1-3rd day; 60, 15-17th day.

Sod. sal. 7 (1.6 %). Salicylate under 60 grs. per diem 4, salicylate 60-100 grs. per diem 3, salicylate over 100 grs. per diem 4, aspirin 1. Total 12 (3.3 %).

# THE VISCOSITY OF THE BLOOD

## A REVIEW

By CLIFFORD ALLBUTT

FROM the time of Vesalius modern investigators have been occupied in discovery of the statical conditions of the living organism, conditions which lend themselves to description and to demonstration: it is the task of our own day upon this foundation to discover the dynamic conditions; but these being in continual flux elude our diagrams, and vanish before they are seen. Nevertheless the mechanics of the human body are being calculated, by such methods as those of Sherrington on the muscular confederacies; of Hales, Marey, Ludwig, v. Basch, and their followers on the arterial pressures and so forth; of Pfeffer, Sanderson, Waller, Arrhenius, Einthoven on the molecular physics—to mention but a few of these pioneers; again, on the chemical physics by work such as that on ‘internal secretions’, or of Starling on the hormones; and on the subtlest biological processes by the researches of Ehrlich and others in respect of such problems as those of immunity. When we realize the swiftness, the counterplay, and the evanescence of these dynamic activities, we admire the patience and assiduity which in several departments have tracked out many of their fleeting phenomena, and calculated their motions. On other lines perseverance has found less reward. In any one of these departments—in the simplest, for instance, that of the physics of the circulation—if much has been done, for the most part these dynamical currents still slip through our snares and escape our reckonings. Considerable, indeed signally successful have been the investigations of a host of observers into the tides of the blood, yet even in the delineations of its massive mechanics there is still much to be desired, while on the chemical and electrical sides of haemodynamics we lack even definite outlines of the molecular activities of the bodily juices, and have attained as yet to few or no principles applicable to practice. However, it is one of the conditions of advance that from time to time we should survey our position; and in the following article I have essayed in respect of the viscosity of the blood some such humble but necessary task.

Viscosity, or the degree of cohesion of the particles of a fluid, as a factor in the efficiency of the circulation of the blood and lymph, has received little attention among English observers. In America, by the work of Russell, Burton-Opitz, and others, this factor is well recognized; yet nevertheless I read last year, in a useful little treatise on arterio-sclerosis by an American physician,

this astonishing sentence: 'The viscosity of the blood, as such, probably has very little effect on the resistance to the flow.' In this sentence what does 'on' mean? and what 'as such'? Can it be that the author believes that the blood runs as freely along its channels as water or alcohol? And a British critic of my studies on the arteries lately bantered me for that I 'still cling to viscosity'. Well, if a man of science may have any prepossessions, I will admit that I 'cling to' gravitation, to the conservation of energy also, and in respect of our present subject likewise to the law or laws of Poiseuille, as to many another theory which has survived by universal consent. And when we know that in a fluid friction must multiply with every increase in viscosity, with every increase, that is, of the cohesion of the particles of the fluid, and when we remember also that nearly 200 times more of the heart's energy is expended in overcoming friction than in direct transference of velocity to the stream, we shall scrutinize most carefully any degrees, however small, in the stickiness of the circulating fluid; for, calibres being constant, these will be multiplied many times in frictional resistance. It is true notwithstanding that in the circulating fluids viscosity may be so balanced as to be virtually a constant; and, if so, may be accepted as on both sides of our equations and currently disregarded. However, the other chief factor in resistance, namely, the dimensions of the tubes, is very far from constancy; on the contrary, under the influence of the nervous system and otherwise, it moves within large limits. Thus relative degrees of viscosity are most difficult to measure; and the standard of it, as a vital condition, is so incessantly readjusted by the protective harmonies of the organism as to maintain it not only in stability, as is the case with the normal arterial pressures, but also in more or less abiding equilibrium. If in some abnormal states the fluctuations of viscosity may be extreme, yet in health, and even under the ordinary evolutions of disease, they seem to be either so confined, or to be so rapidly readjusted, as to elude our relatively clumsy methods of measurement. Even in the laboratory the physiologist has made little progress in this research, his results are as yet far from consistency; and the methods are still farther out of the reach of the clinical physician. For these reasons then, since in 1898 (Lane Lectures) I set forth the essential importance of viscosity, I have refrained from discussing it; but have attended rather to the fluctuations of vasomotor tone and of alternative irrigation areas, which probably oscillate within much larger limits and under simpler conditions, are therefore clinically more perceptible, and afford more consistent records to our still imperfect instruments.

Far then from concentrating my attention upon viscosity, I have not gone beyond occasional allusions to it, which however, as against a customary neglect of this factor, may have appeared to my readers as comparative emphasis. And indeed this factor can never be far out of our thoughts, for if it should appear that in states of disorder viscosity may vary considerably the consequences cannot but be heavy; the handicap upon the heart must be enormous. So while giving my own time to those clinical phenomena for whose appreciation I am better equipped, I have also collected for some years what I could find in

the researches of observers skilful in the measurement of physical coefficients, and have tried to piece together such approximations to knowledge as from time to time they have offered to us. Quite recently Determann, whose researches in this field are well known, has published a tract (13) of larger scope, the first treatise, I believe, devoted to the subject; and to it I am greatly indebted for the revision of my own notes, and moreover for the example of a lucid and adequate comprehension of the whole matter so far as it has been carried.

*Of methods* it would not become me to seem as of my own knowledge to speak; my own experiments have been of no importance, and those which I have witnessed have been comparatively few. What are the difficulties and the fallacies of the research we shall see presently; difficulties with venesection (in man), with the coagulation of the blood, with its gas content, with changing temperatures, and so forth. Hürthle's method, valuable as are his results, is applicable only to animals. Hirsch and Beek's viscometer, which is generally used in Europe, requires not inconsiderable quantities of blood, and takes it in the venous state, a state in which, as we shall see, it is of higher viscosity; whereas we desire to know the blood as the left ventricle lifts it. The earlier viscometers did not provide for constancy of temperature; but in his last model Determann, by jacketing the tubes, aims at this constancy; and, moreover, to provide blood enough for the estimations by a simple puncture of ear or finger, as in his instrument 0.2 grm. is sufficient. The comparison of glass capillaries with the fine blood-vessels, and the safety of the inference from the one to the other, have of course been thoroughly discussed by all experimenters in this field; and in this respect the technique may be trusted, for it is ascertained, by noting on the blood column in the aorta of freshly killed animals a concave meniscus formed by adhesion of the blood around the wall, that the blood does wet the wall of an artery, and that it does not slip; or if it does that the slip is occasional and negligible. And in the peripheral vessels pulsation may be neglected, as in them oscillation is merging into a continuous flow. The term 'capillary tube' is not physiological; it does not signify identity of diameter with the capillaries of the circulation, but tubes of small if not constant diameter in which fluids behave otherwise than in large or middle-sized channels. Of course in full tubes there is no 'capillary attraction', as this attraction lies between contiguous surfaces of fluid and air, or of two fluids of different qualities. However, to eliminate any fallacy of tube diameters, Determann in his estimations has frequently used in the same experiment tubes of three calibres; namely, tubes traversed by water in 7.6 sec., 12.3 sec., and 58 sec. respectively. He finds, however, that within these limits the calibre of the tubes is negligible. Tigerstedt (34) agrees with Hürthle and Hirsch and Beek that Poiseuille's law may be said, with very slight margin of error, to express the hydrodynamic processes in the circulation.

As regards the interference by the coagulation of the blood, it is believed that during the first moments of venesection the blood does not undergo

substantial alteration; still under this condition the observation must be made too rapidly for careful work, yet defibrinizing agents—such as oxalic acid—may alter its qualities considerably. Determann uses hirudin in minute quantity, but it is suspected that even this agent may interfere with the normal properties of the blood; certainly it facilitates the precipitation of the corpuscles. In the case of animals the anaesthetic also may have some modifying effect. In chloroform narcosis it is said that the viscosity of the blood rises. Walter Hess (19) in his instrument, by fixing two glass capillaries parallel and near together, enables the observer to compare the rate of the blood under examination with that of a flow of water.

Experimenters then are as yet far from satisfied with any one of the various viscometers hitherto invented; and Adam (1), in the laboratory of W. His of Göttingen, whose work in this field gives weight to his opinion, thinks that instead of advancing to a greater simplification, as is usual in instrumental progress, these instruments, if they are to meet the many and various contingencies which are inherent in the nature of the research, must become more elaborate. For we are baffled not only by the delicacy of the mechanics of the matter but also, and yet more, by the infinite complexity of this and the kindred problems in their physical, chemical, and vital potencies. It is true, however, as we shall see presently, that these kindred qualities offer to us in electrolysis, in refraction, in osmotic pressures, and in chemistry, alternative and controlling methods of measurement.

For with the mind's eye let us endeavour to obtain a vision, or a glimpse, of these myriad and infinitely various modes of energy, streaming forth in all dimensions of space throughout the animal body; forces so fleeting and yet so perennial, so intricate and yet so harmonious, so universal and yet so nicely specific, so subtle and elusive, yet so mighty. We live but on the balance of them; in their spring so swift, so quickening, yet ever implicit with the cadences in which they are to vanish when the symphony is over. With a pertinacity which indeed is born of them we, with our microscopes, our manometers, our viscometers, our electrometers, our polarimeters, year after year are scheming diagrams of their mazes, plotting out their centres, their rings, and their chains, threading them now and then and here and there, aiming at some exact measures of their features; streamlines tensive, diffusive, osmotic, ionic, chemic, and, what we are fain still to call, vital; the dynamic salts permeating and spinning the more static colloids, and passing them by evanescent phases from suspension to solution and oxidation. Nay, how vain it is to try with words to paint these influences! every molecule a world, every cell a solar system, every organism a prismatic fountain of strength, animation, and immeasurable purpose! Vain indeed are such words, and yet without them, without some endeavour to express this vast and multitudinous rhythm, this mazy and symphonic dance, we might isolate one by one diffusion, osmosis, ionic stresses, gaseous tensions, and so forth, as we might pin out upon a board the several items of the body—its bones, its tendons, its nerves, and yet form no vivid conception of its

functions as a whole. And if we do attain to any vision of this unity in complexity, of the poise of these bewildering rhythms, in our first marvel at this infinite complexity of harmonious energies may we not recoil as Darwin, in his amaze at the beauty of the human eye, recoiled in momentary incredulity from his own theory?

A certain effect, or expression rather, of this concord of infinite velocities and exchanges is that we can seize no moments of arrest during which by our machinery static measurements can be made. Not having the cosmic eye nor infinite mind, we halt between arbitrary classification and functional jumble. If from phase to phase fluctuations must be, or may be, large, they are consentaneously held up again; still unless, on account of the fragmentary outlook of the human mind and of other limits of its faculties, we can after some arbitrary manner catch them flying, and get some kinetographic records of exposure, we must give up the hope of attaining to a scientific knowledge of the functions of the circulation. If the viscometer cannot become a handy clinical instrument, yet the clinician must demand from the physiologist some approximate calculations of the potent if not dominant factor of viscosity. If it be in health always and commonly in disease so incessantly equilibrated as to be virtually a constant, so much the easier for us; but nature does not usually make scientific measurements so easy, and we shall not be satisfied to assume this constancy—at any rate not in states of disorder—until laboratory experiments convince us of such uniformity or approximation. Certain well-known observations of George Oliver suggested that under high arterial pressure the space relations of blood and lymph are altered, and therewith the density of the circulating fluid. The younger Erb (17) also came to the conclusion that with rise of arterial pressures the blood concentrates—contains more solids; and that as pressures fall it becomes more dilute; though this reaction is slower than the previous concentration. From this point of view two papers read to the Royal Society by Mallock (Nov. 24, 1910) are of interest, in which he demonstrated that in 'viscous flow the character of the stream differs according to whether the flow is towards decreasing or increasing pressure'. However, subsequent observers think that such changes are not due, or are not notably due, to mere exudation and return of lymph from the blood-vessels; and that the ebbs and flows of blood-distribution in areas predominate over those of lymph filtration. Besides, such and so free are the molecular reciprocations amid all the bodily fluids that in these respects the lymph, which is actually the medium of the cells, may be taken as the equivalent of the blood; indeed Botazzi (7) and his pupils seem to have proved this upon animals, so that little or nothing is to be gained by separating blood and lymph as one of our necessary if arbitrary divisions of the subject.

What analytic divisions, then, can we conveniently make? In the first place our experiments are restricted to capillary, or virtually capillary, tubes, concerning the physics of which, by the labours of Poiseuille and others, we are instructed already; and within such tubes in the body it is that the circulatory

frictions are most tenacious. The currents in larger vessels are affected by other conditions. As we approach the peripheral areas we find the resistance rising rapidly. And in the blood it is of great importance to watch not only its behaviour as a whole, but also, dividing the corpuscular elements from the plasma, to calculate the viscosity of the plasma and the blood severally. By the corpuscles themselves, merely as foreign bodies, the viscosity of the blood is largely increased; but we shall see that this effect of them is much more complex than that of indifferent foreign bodies. Another chief division in our analysis speaks for itself; namely, the distinction of the colloid from the saline constituents, each class and each phase of which behaves in ways of its own.

On these lines we have to try to reach some vision of the infinite reciprocal play of the modes of energy in which the living web of life is ever spinning; but in this vision we perceive that the influence of contingency must be incessant, and in our experiments difficult to neutralize. Let us glance at some of them. We shall anticipate rightly that the molecular dances will be different at different *ages*, and may be different in the *sexes*. Again, animals and plants will differ from each other and from man; and in our experiments we can keep animals in respect of external conditions far better in equilibrium than is possible with man. In youth it is fairly certain that the capillary wall, and other membranes concerned, are more permeable than in age; and herein may lie some or much of the lagging of function in the elderly, and again perhaps some of the stiffening of blood-pressures in them. By experiment upon 122 persons divided in age by decades W. Hess (20) showed that the viscosity of the whole blood rises from childhood to adult life, and perhaps towards middle life; but that after maturity, the variations show no consistent progressive or retrogressive tendency. The mean of adult males was 4.74 (water is the unit); the extremes were 4.0 to 5.5: of adult females 4.40; the extremes 4.0 to 5.4. The viscosity of men seems thus to rule higher than that of women, at all ages. A viscosity in a male below 4.3 or above 5.3, and in a female below 3.9 or above 4.9, Hess would regard as abnormal. Probably the irregular variations lie in the varying percentages of haemoglobin. Nevertheless, even if the viscosity figure be within limits of the possible normal, and indeed if also the haemoglobin figure be not positively abnormal, yet, according to Hess, if the quotient  $\frac{\text{viscosity}}{\text{haemoglobin}}$  be outside the limits of 17-21, the condition is abnormal. To the haemoglobin factor we shall return.

There are other difficulties also in defining the *limits of the normal*. In woman, for instance, is pregnancy, is menstruation, within the normal? Ribaudi (32), using Hess's instrument, found in pregnancy a fall of the viscosity of the whole blood, especially in the latter part of it, until just before parturition, when it rises—especially if the birth be a hard one, or in eclampsia—to fall immediately after delivery. The viscosity of the blood is higher in the foetus than in the mother. During suckling the viscosity of the maternal blood does not rise. Similarly there is, he says, a premenstrual rise of viscosity, a fall during



menstruation, and a rise to normal immediately after it. Again, idiosyncrasy plays its part, perhaps a considerable one; between various species of animals Hürthle found such differences; dog's blood he found about 4.7; cat's blood about 4.2; rabbit's blood about 3.3 (24). Then again there are certainly fluctuations during the day, effects of meal-hours, exercise, diet, nervous influences (especially vasomotor), and so forth. Climate and altitude likewise have, as we shall see, their effects on the viscosity. I shall not quote many figures in these inquiries, for as yet the discordances of various observers give us no firm ground for generalization from them. Concerning effects of diet upon the blood-viscosity, if some definite conclusions could be formulated they would be very helpful to the physician; but the reports are discordant. Hürthle and Burton-Opitz, upon animals, inferred that changes of diet were reflected largely in the viscosity curve, even in variations so large as 20 per cent. Determann, on the contrary (in man), comparing vegetarian with animal diet, strictly observed for some days, failed to convince himself that these extremes became perceptible in terms of viscosity. It seems to me that the blood in gathering and selecting its own materials out of the food-stuffs may well neutralize irregularities of supplies, at any rate for some days; proteins are to be got out of either diet, and extremest variations in electrolytes, e. g. salts, are probably of more importance. In our everyday work much must depend on such adaptations, though over much longer periods—a year or a decade of years—more permanent alterations might become established. We shall see that in plethorics with high blood-pressures Determann himself has noted a higher viscosity. Moreover it appears to me that comparisons between carnivora and man may be invalid in this respect. It seems likely that in dogs, for instance, the viscosity of the blood would fluctuate more violently on conversion to a vegetable diet than in omnivorous man. I fear the pig would present more of a parallel with ourselves. In the careful and repeated experiments of Burton-Opitz the most definite results seemed to be that in dogs pinning (presumably water was given to them) reduced viscosity, and full flesh-diet increased it; in rabbits that viscosity varied more with the watery constituent of the food. Feeding and fasting would seem to offer more crucial differences, though it is not easy to determine the optimum moment of cell satiety. It seems certain that meal-hours determine some fluctuations of viscosity; and they seem to be larger in the morning than in the evening, the daily excursions being about 12 per cent.; now in experimental estimates these normal daily waves must not be forgotten.

Concerning *work and exercise* the evidence is less conflicting. Sweating, it is agreed, raises viscosity by about 1.25. Apart from this factor, Blunschy<sup>1</sup> found from his own and from other experiments that prolonged exertion, such as ski-running, reduces viscosity considerably, while short forced efforts raise it. Notwithstanding it was found that by derivation from the tissues a reduc-

<sup>1</sup> Blunschy's paper was a Zurich dissertation of 1908 of which I have seen extracts in year-books, and other quotations. His curves of normal daily fluctuations, &c., are republished in Determann's book, p. 66.

tion towards the normal is soon brought about (Lommel (27), Hess, &c.). Böhme (Kiel), speaking in a physiological discussion<sup>2</sup>, said that brief severe exertion (on the ergostat) concentrated the serum, the albuminous content rising 7-8-8½ per cent. It returned to normal in about five minutes. He explained this by the higher osmotic pressure in the muscle during work, the water passing into the muscle. An important feature of these, and of some other careful experiments, is that relatively large figures are registered, so that there is room for some experimental error. For instance, on long marches as much as 13.46 per cent. of difference has been recorded; an estimate which ought to leave a substantial result of 7 or 8 per cent. And Hasebroek, in a very interesting discussion at one of the German Medical Associations (18), observed that in estimating blood pressures during exertion, to avoid fallacy he had to estimate viscosity also; a correction in which Deneke agreed. Blunshy also, on this occasion, referred to his own experiments (quoted above), and added that during bodily exertion he had noted movements of pressure and viscosity to be parallel; and for us clinical physicians the important factors, with blood of constant value, are its speed and the heart work expended on it. Hasebroek indeed expressed the opinion that Oertel's therapeutical methods owe more to reduction of viscosity than to reinforcement of the heart itself. He found also, as we have found in England, that on the whole, in trained men, by continuous exertion the arterial pressures are reduced.

*Climate* is too large and vague a condition to detain us at present; but in *altitude* we have a more definite factor, and one for which we have some more definite data. Determann and others have found that at high altitudes viscosity increases substantially; this is due, at any rate in part, to increase of red corpuscles, a matter to which we shall return presently; and we find the same rule in cyanosis, in which these corpuscles more abound. It is well ascertained that the blood of normal residents in high altitudes, such as St. Moritz, is richer in red corpuscles; they have probably a more capacious blood-making apparatus and lung capacity. It is in these persons that Determann finds a corresponding excess of viscosity (by 17.4 per cent.); and v. Korányi has found that this amount can be reduced by the inhalation of oxygen. To this condition of altitude I shall return later.

The *density and volume* of the several secretions and excretions of the body, difficult as they are to follow, are yet much concerned in the problem before us; for presumably by their fluctuations the equilibrium of the corporeal fluids is largely provided. When, for example under a sweat, the viscosity of the blood rises, and is compensated by derivation from the tissues, the canals and reservoirs of the system will give up some of their aqueous element; and in some measure the electrolytic element also will be readjusted. It has been my own experience, and I believe that of mountaineers generally, that during long climbs one does not desire much food; nor indeed is it wise to eat largely or too soon after coming home, for the secretions of the parts of digestion have rendered

<sup>2</sup> Reported in *Deut. med. Wochenschr.*, May 5, 1910.

up their juices to prevent concentration of the arterial blood, and therewith increased labour of the heart. The scantiness of the urine and the dryness of the mouth in prolonged exercises are familiar to every one.

So far I have sketched out the sort of influence exerted by outward conditions upon the viscosity of the blood; I may now ask the reader to follow me in pursuing this train of thought into the motions, qualities, and exchanges within the blood itself. This part of the inquiry is traversed by certain important but indeterminable factors, indeterminable at any rate by handy methods. Two of these factors, not easily to be appreciated during experimental observation, are the velocity of the blood-stream, and the output of the left ventricle. Until these moments can be reckoned in, our observations must still have something conventional about them. Meanwhile, however, we may make a little progress with other conditions on which they have some dependence.

And this seems to be the place to point out that viscosity is not *specific gravity*, an assumption not infrequently made even by eminent writers on the circulation; there is not even a direct relation between these two coefficients. A normal or even a high specific gravity is not inconsistent with a low viscosity. The 'strong salts' and the 'weak salts' differ widely in molecular weight, and accordingly in the effect of equal doses. Of the solid constituents of the blood some, such as sodium and calcium chloride, have in respect of viscosity a positive effect; others, such as sodium iodide, a negative. Again, as we shall see, the gas content of the blood largely affects its viscosity; by carbonic acid this is increased, by oxygen it is reduced. But I may digress for a moment to point out that the specific gravity is by no means a negligible factor. A long series of observations by Roy, Lloyd Jones, and myself proved that in the normal man the specific gravity is maintained fairly constant, being 1058-60; but, in males especially, it tends after the age of forty to fall. If in the elderly it rises, the rise is often coincident with a rise of arterial pressure also, in which case cerebral haemorrhage is to be feared, and may be prevented. In Hyperpiesis I have never found this variable to be subnormal, and if pressures fall the specific gravity falls likewise. Conversely, if in a case of suspicion of cerebral haemorrhage the specific gravity be low, the diagnosis—as in respect of embolic or thrombotic alternatives—should be revised (Lloyd Jones and myself). In this case the arterio-sclerosis will probably be of the kind which I have called involutionary or decreescent, as opposed to that ensuing upon prolonged high pressures. At the same time, although in a case of arterio-sclerosis, or high arterial pressure, the specific gravity be high, or rising, and haemorrhage be feared, yet a falling specific gravity may not be propitious, for if not consistent with cerebral haemorrhage it may signify failing reactions. For instance, to return to viscosity, Hirsch and Beck have shown, contrary to the presumption of Ewald, that if in the earliest stage of granular kidney—the disease above all in which peripheral resistance is high—viscosity may rise, it soon falls, the fall being probably due to hydræmia. But the whole question of molecular concentration in the sundry kinds of renal disease has yet to be dealt with.

Generally speaking, in later life falling arterial pressures are attended with falling specific gravity. Specific gravity then is no test for viscosity; indeed the relation of the two factors often moves inversely (10), and each factor must be separately measured.

Now, having cleared our path by making these distinctions, let us concentrate our attention again upon viscosity itself, which, signifying *internal friction*, must be a cardinal factor in the circulation of the blood; indeed were the small vessels of constant calibre, area, and ramification, it would be a tyrannical factor. The law of flow in capillary tubes—known as Poiseuille's law—is this:—That at a constant temperature the quantity of flow of water in unit of time is directly as the pressure and as the cube of the radius, but inversely as the length. With the cone of outflow and the vena contracta we have not to deal, except to remember that this cone is the expression of the section of the flow; for the flow is regarded as consisting of cylinders of increasing velocities, the one within the other. The outermost cylinder, that in contact with the wall, if it wets the wall, as in the blood-vessel we have seen that it does, is stationary, it changes by diffusion only; but from this cylinder inwards the successive layers, or cylinders, of the fluid travel each over the other with increasing velocities as they lie nearer to the central or axial cylinder, and farther and farther from the more and more sluggish peripheral cylinders. Thus we see why the outflow is conical. Now as each of these cylinders is continually engaged in shearing stresses in relation to the pair without and within it, the stickier the fluid the more the internal friction, and the harder—*caeteris paribus*—the heart must work, if the velocity is to be kept up; for much of this friction is turned to heat or other modes of energy, and, so far as velocity is concerned, is lost. If then in man the viscosity of the blood is four to five times that of water we may apprehend how enormously more is the energy required to circulate blood than water; and how severely, *caeteris paribus*, the heart will be handicapped by even small increases in this viscosity in beds of friction so extensive and so ramified as in the vessels of upright man: *caeteris paribus*, I repeat; for, according to the law we have accepted, the cubes of the radii of the tubes and their lengths, variables of wide limits, have to be reckoned with also. I may point out here that as friction takes up 98 per cent. of the heart's energy, and as again friction varies as the cube of the radius, a very slight increase of radius will make a very large fall in resistance. And we must not forget another obscure factor, namely that it is in the capillaries that the work is done; there the physiological exchanges take place between the nutritive juices and the cells, which can scarcely be without some effect ('Gewebsgefühl') in speeding or delaying the blood. This effect William Broadbent believed, in some morbid conditions, to be a considerable factor in delay of the blood in the capillaries. And we shall see that the gas content is a large factor of the velocity of the stream, or at any rate of the viscosity.

*The blood not a homogeneous fluid.* Hitherto the blood has been taken as if it were a homogeneous fluid, as it were water thickened more or less with

glycerin. But we well know that such is not its condition; that in the plasma colloids and saline matters are mingled, and that in the plasma are suspended a large number of corpuscles, red and white. Now if we suppose these bodies to be equally distributed throughout the fluid, and to be of constant diameter, would such a compound stream behave as if homogeneous? In making the comparison the clotting embarrasses us; in defibrinized blood the corpuscles sink before the observation can be completed, and the addition of chemical agents to delay clotting presumably interferes with the reaction of the blood thus treated; even Determann's parsimonious use of hirudin is declared to be open to a similar demur. Mott (29) has suggested that nucleo-protein, as it has so rapid a coagulative action on the blood, 'may have a viscosifying effect on the blood.' And Arthur Bodington, in his Cambridge M.D. thesis for 1903, expressed a similar opinion. In this place a description of the various methods by which these difficulties have been surmounted, or reduced, would be inappropriate; suffice it to say that expert observers, such as Beck and Hirsch (4), Hürthle, and Tigerstedt (34), are agreed that in respect of Poiseuille's law the blood may be considered within small limits of error to behave as a homogeneous fluid. Notwithstanding this approximation, it is of great importance in our analyses, as we shall see, to reckon severally the part played by the plasma and by the whole blood. Of laking the blood we will speak presently.

The plasma consists of colloids suspended, and merging by infinite degrees towards solution, in the serum; this again consists of a solution of salines and proteins on which its physical properties depend. The plasma without the corpuscles is of course of lower viscosity than the blood as a whole; but the viscosity of the blood depends not on the corpuscles only but upon the plasma content also; and in this more upon the colloids than upon the salts, some of which are negatively viscous. The viscosity of the whole blood is higher than that of a mixture of the corpuscles in the same proportion with salt and water. Moreover, if the corpuscles are not uniformly diffused, viscosity will vary in areas, rising in those in which the corpuscular content is denser, and falling in those in which it is scantier. Thus the rise of viscosity in asphyxia may be due to the more numerous corpuscles, or to variations in size; but here, as we shall see, the effect of carbon dioxide comes in. That in leucoeytosis or erythrocytosis viscosity must rise seems an obvious inference; and although total blood-volume is increased, this increase in cases of profusion of reds is in less relative proportion. In two cases published by Parkes Weber (37) in which the red cells attained 8-8½ and over 10 millions respectively, and the haemoglobin 200 per cent., although the blood-pressure (full systolic?) was only 160 [a rough mean between Haldane's Riva-Rocci (157 mm. on two observations) and Weber's Hill and Barnard (165 mm.)], the viscosity was such that the heart, in spite of this moderate systemic pressure, was failing, at the age of 29, under the aggravated friction thus engendered, and the considerable (in the second case 75 cm. per 100 gm. body weight) excess of total blood-volume to be driven. Hutchinson and Miller (25) in a similar case recorded a high

degree of fibrosis of the vessels, which they reasonably attributed to the high frictional resistance of  $7\frac{1}{2}$ –8 million reds; an observation which favours the assumption that viscosity is at least a *vera causa* of arterio-fibrosis; Craig's Cambridge M.D. thesis on excessive arterial pressures in a certain kind of melancholia is well known; Bruce and Alexander (9), on these high pressures in such cases of insanity, say that these pressures (of 140–180 mm.) are associated with a leucocytosis. It occurred to me that in the high viscosities of polycythaemia the heart should be enlarged on both sides: but, in such notes of the few autopsies I can lay my hands upon, the heart is spoken of in general terms only, as hypertrophied or dilated. It is to be desired that in future the state of the several chambers of the heart should be carefully noted on Müller's method. It is also to be desired that when the circulatory corpuscles in such cases are reduced in number, as for instance under therapeutical methods, that the effect on blood-pressure, and, if possible, on velocity, should be accurately noted. When a rise of arterial pressure is due preponderantly to large areas of vaso-constriction the stress, as in granular kidney, will fall upon the left ventricle in corresponding degree; if, however, the resistance be due to increased viscosity the stress should be felt alike on both sides of the circulation. It is said that in granular kidney, unless in the earliest stage of it, the viscosity of the blood is not much increased, if at all (23), a notable fact when we consider the polyuria of the disease; now it is in granular kidney that hypertrophy is developed often wholly, always very preponderantly, in the left ventricle. It may seem surprising at first sight, if the corpuscles be so large a factor in viscosity, that in the cases of heavy polycythaemia to which I have referred the arterial pressures do not rise enormously; but certain compensatory adaptations seem to meet the stress, amongst which vaso-motor dilatation must take a principal part. I have pointed out how large must be the effect produced by a small increase of arterial radius. Yet if such a dilatation yields a cubic increase of space, it may not thereby neutralize the extra burden of the heart (22). How perilous, how fatal, enormous increases of the corpuscles, or relative increases, may be is illustrated in certain colliquative diseases, such as cholera; in which conditions also the marvellous effects of intravenous injections of saline water in reducing the viscosity are conspicuous: and these cases are probably but eminent examples of an injurious process which, in many diseases, especially in fevers, may constitute a considerable if occult cause of danger to life.

I have already hinted that in the viscosity of the corpuscles there is more than the mere friction of multitudinous foreign bodies. We are apt to forget in the discussion, not only of this mechanical question but also of associated physical questions, that the surfaces of the corpuscles are bathed in the plasma, wet with the colloid fluid in which they are suspended, and so far partake of its qualities. But there is a simple method of ascertaining the mere mechanical conditions of these solids by elimination, that is by *laking the blood*; in laked

blood we have an opportunity of observing what effects, other than by mechanical suspension, the corpuscular elements may have on the physical reactions of the blood; by their stroma, for instance, their haemoglobin, their gaseous content, and so forth. Determann (14), Adam (1), Hess, Blunschy (5), have given especial attention to these functions, which seem to be after this manner. Laked blood proves to be not less, but more, viscous than normal blood; and for this reason, that the corpuscles contain within them a substance still more viscous than the plasma, which, while inside them, is prevented from exercising this property to the full. Thus it falls out that in the blood when laked the molecular friction in the relatively homogeneous fluid is higher than between the corpuscles and the serum. The explanation seems to lie with the stroma, which, segregating into granules (Adam), sets up more friction than do the bodies of the original corpuscles themselves. On removing these suspended bodies by the centrifuge Adam found the friction considerably reduced.

But this is not all; by another series of experiments these industrious observers proceeded to demonstrate that, even after the removal of the stroma, there was still a notable excess of viscosity; and this they have traced to the compound coefficient of haemoglobin and gas content. Oxygen and carbon dioxide, which produce no effect of viscosity upon plasma deprived of corpuscles, affect its viscosity instantly when to it are added crystals of pure haemoglobin. We see at once then that in laked blood this compound factor comes into full activity, and how important it is in these comparisons to know when testing viscosity if the blood was taken from a standard area; if venous, capillary, or arterial.

Here comes into view then a most important condition in disease, especially of disease of the lungs or heart, namely that excess of *carbon dioxide* (15) means excess of viscosity. Thus, in defective oxidation, at the moment when the velocity of the blood should receive a compensatory acceleration, its viscosity is rising. It is a familiar experience with me, as I doubt not with my brethren, that although on the mere mechanics of pulmonary respiration it may not always be easy to explain the beneficial action of oxygen inhalation in cyanosis, yet in many instances the patient clings to his oxygen-pipe with affection, or even with desperation. Now if access of oxygen favours an attenuation of the viscosity of the blood, it should thereby ease the heart and forward the blood-stream; if accumulation of carbon dioxide makes for an increase of viscosity and a sluggish current, the comforting effect of oxygen inhalation becomes intelligible. The principle can be demonstrated readily as follows:—Some blood is drawn from a vein and, to prevent coagulation, a very little hirudin is added, and the viscosity tested. It is then well shaken in air, to oxidize it, and the viscosity again tested, when it will be found to have fallen considerably. And besides this relief by oxidation, we may presume in the body on some farther fall in friction by a diminution in the number of red corpuscles; for these in defect of oxygen multiply, in increase of it are reduced in number. In heart disease von Korányi has shown by blood-counts that

inhalations of oxygen and a rise of tension of the gas in the blood are followed by a fall in the number of reds.

It would seem indeed that of all factors of viscosity carbon dioxide is the chief, for the changes of viscosity by these gases are less of the plasma than of the corpuscles; so that in diseases of the heart and lungs, as Determann says, a vicious circle is established of plus viscosity, plus resistance, plus  $\text{CO}_2$ , and so round to plus viscosity again; a gyration which the heart may be unable by increasing the velocity to break through.<sup>3</sup> Still as in life there is no direct relation between arterial pressures and viscosity, for indeed they may move contrariwise, evidently some large compensatory factors of another kind must be at work, probably vasomotor, but of which we have as yet no accurate knowledge; so that this problem is far from solution, and so will be until we have some ready clinical means of ascertaining cardiac output, velocity of current, total mass of the blood, and breadth of peripheral bed.<sup>4</sup> We should suppose, however, that cases of high pressure plus viscosity would favour cerebral haemorrhage, of low pressure, thrombosis. And although, as we have seen, under these conditions the corpuscular changes are the main factor in viscosity, yet the behaviour of oxygen and carbon dioxide are not exactly reciprocal. Viscosity depends so far on the state of the plasma that it cannot be measured simply by the number and sizes of the corpuscles; but presumably the blood grows more and more viscous as it approaches the lungs. Oxygen combines with the haemoglobin to form oxyhaemoglobin, but is not very stably fixed; while carbon dioxide attaches itself not only to the reds but also to other constituents of the serum, as to mineral alkali and protein bodies. Hydraemia again must often be an interfering factor, and one difficult to estimate. An excess of  $\text{CO}_2$  favours the penetration of chlor-ions and water into the corpuscles, with a corresponding movement outwards of albuminoids; and a consequent rise of viscosity dependent in part on increase of colloid in the plasma, in part on swelling of the corpuscles; at any rate such is the reaction *in vitro*, and it is consistent with certain experiments *in vivo*. And when we may have ascertained the values of these factors for the blood in general we must still remember that the states of the blood, and the interchanges between blood and tissues, may vary widely in the several areas. Again, although any two or more qualities of the blood taken separately may lie within normal limits, yet their quotient may be abnormal, as illustrated by Hess's statement, already quoted, that even if haemoglobin and viscosity taken separately may lie within normal extremes, yet if these figures divided give a figure which does not fall within 17-21, the blood is of abnormal composition. Bachmann,<sup>5</sup> working with Hess and Eickhorst at Zürich, gives

<sup>3</sup> On this aspect of the matter, see also Bence, 'Visk. d. Blutes,' *Zeitschr. f. klin. Med.*, 1906, lviii.

<sup>4</sup> Haldane and Lorrain Smith's carbon monoxide method is not for clinical work; and that of v. Plesch, if more readily applicable, seems to be open to some adverse criticism; *vid. Müller, Deutsch. Arch. f. klin. Med.*, 1909, xxvii, 559.

<sup>5</sup> *Deutsch. Arch. f. klin. Med.*, Oct., 1908: a careful paper with observations on 400 cases.



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What part *filtration* may play in these animated processes is uncertain, for the data of relative local mechanical pressures, and of the distribution of gases, are out of our reach, at any rate at present. We recognize filtration in certain areas, as in the renal glomeruli,<sup>8</sup> and it may be no inconsiderable factor elsewhere; but *diffusion and osmosis* are universal, and govern the balances of viscosity; so that the nutrition of the cells and the mechanical ease of the heart and circulation are favoured by isoviscosity and isotony, as these in their turn are regulated by the bywash of the secretions and excretions, and probably under some influences of innervation. And these reactions with the tissues are by no means confined to blood and lymph, but are incessantly at work also in the blood itself between its plasma and its corpuscular elements. Such here and there are the peeps we may get into the intense and immeasurable reciprocations of these biological functions in health.

Chemical analysis in the ordinary sense, although it gives us indispensable information as to the ultimate and mediate components of the blood and lymph, throws no independent light upon their physical attractions and repulsions, and gives little insight into the physical and electric vibrations which constitute the dynamics of these fluids. We shall see, however, that we are not wholly without a method of measuring these activities, for in *electrolysis* we have a means of ascertaining approximately the rate of osmosis, and indirectly even of molecular friction. Hampered as we are by the imperfection, or alleged imperfection, of viscometers, it will be well to attack these problems for a while by way of the electric resistance of the blood. The mean normal resistance at 15.6° C. is 550 ohms (D. Turner), the specific resistance 93.5. Dawson Turner, of Edinburgh, (35) made a number of experiments to ascertain the time occupied by sodium chloride to reach the blood. In five cases the blood-resistance was measured before taking 30 grains of the salt, and at five-minutes' intervals afterwards. The average time taken for the first lowering of the resistance of the blood was 15.4 minutes, and for the maximum effect 21.4 minutes. Dr. J. Edmunds, of Ann Arbor, also told me (in September, 1907) that by interposing a length of the femoral artery between two hooks connected with positive and negative poles, and recording the variations of conductivity of the blood, he was enabled to observe the intervals, which were very brief, between his injecting a saline solution into the jugular vein and a consequent rise in the conductivity of the blood.

The tests of *freezing and boiling points*, as we shall see, have proved disappointing in practical medicine. For instance, the milk and the serum of the cow have the same freezing-points, but the electric conductivity of the milk is lower, because it contains relatively more organic molecules. Furthermore, not all the inorganic particles in these fluids are in full electric activity, for some, combining with proteid substances (Loeb's ion-proteids), exert less electromotive

<sup>8</sup> There seems to be some evidence indeed that the glomerular function is not one of mere filtration.

and osmotic energy. It is not then the number of ions but their rapidity, their driving power against the indifferent colloids, which is of working importance. And here we observe again the irrelevance in these measurements of the specific gravity. Speaking generally, colloids are of low electric conductivity, salts of high conductivity; but salts, as we have seen, are far from being of equal effect on viscosity or conductivity or on the freezing-point. The specific ionic effects of the various salts are not identical. Some raise viscosity; others, such as the iodides, reduce it. We may regard the salts, then, as incessantly bombarding and penetrating the colloids, thereby promoting the various dynamic activities in the fluid, from diffusion onwards. Thus viscosity is diminished; and at temperatures higher than the atmosphere, but under that of incipient coagulation, these reactions of colloids and saline are more and more active. We have seen that globulin insoluble in water becomes soluble in weak saline; and Pauli (31), obtaining by careful dialysis a neutral albuminous solution, found on adding to it gradually small increments of salt (sodium chloride) that the viscosity did not rise, but fell. He explains this paradoxical reduction of inner friction by adding solids on the supposition that particles of salt, by attaching themselves to the albuminous molecule, form a more slippery albumin-salt-ion combination. Yet we shall have to admit presently that in practice the viscometer fails to register any fall in the blood of patients under treatment with the ordinary doses of iodide of potassium. We must not, of course, regard the flow in glass-tubes as identical with that in the fine arteries, but, as I have said, the approximation is found to be fairly representative; but it may be that in the body the exchanges between the fluids and the cells, and the vasomotor readaptations, are so rapidly compensatory that we fail to catch the oscillations. In like manner under iodide of potassium no fall of arterial pressure has yet been proved; though the belief of clinical observers, for what it may be worth, is very prevalent notwithstanding that by the administration of this salt the circulation is eased.

*Diffusion*, under the circumstances of which we are speaking, is a universal factor: and in colloid fluids particularly efficient, for thick fluids of differential densities lend themselves less readily to mere mingling. We remember that it is by diffusion only that the stationary outermost cylinder of blood which wets the wall of the vessel is continually being changed. It is true that colloids are of low diffusibility, but by the salts their diffusion is promoted; and the modern physical chemists find that, in respect of diffusibility, substances in solution behave as gases. Thus by variations in kind and quantity of saline content, some salts being positively, others negatively, viscous, continual activity in the blood is provoked; the proteid or colloid particles continually sliding along lines of least fractional resistance and, as it were at their thin edges, passing fractionally from suspension into solution. In an area of the circulation diffusion depends also, of course, on the velocity of the stream in that area.

To attempt to pursue the several lines of these researches, the mechanical,

the electrical, the chemical, would carry us beyond our present purposes; and it must be accepted that in the process of biological analysis the separation of the modes of energy by which the tissues of the body are woven, repaired, and demolished, and the concentration of the attention upon each severally, is an arbitrary convention by which we endeavour, and indeed are enabled, to apprehend and discriminate the lines and degrees of energy; yet in these partial reckonings we are not to forget the whole, not to lose comprehension of the blend of these various aspects, the merging of these functions the one into the other, the unity in complexity. Thus, in passing on from the mode of energy which we have called diffusion, the steps by which we advance to osmosis are imperceptible; and onward again in the discussion of osmosis—i. e. the selective absorption by membranes from fluids, as contrasted with filtration through hypothetical pores—we shall soon find ourselves involved in certain other functions, or aspects of function, which under analysis must receive their several expression and recognition, such as the electrolytic or refractive coefficients; as also in certain other conditions, such as resistance, pressure head, velocity; and in certain other properties, such as volume, molecular and atomic weight, and so forth; in many forms of ubiquitous and protean but harmonious modes of energy, incessantly transforming themselves the one into the other. Thus we may often interpret one by the other, as osmosis by refraction, or by electro-conductivity; and thus it is that by electrolysis we obtain one more sorely needed method of measurement, electro-conductivity and osmosis being terms either mutually convertible, or of the same significance, the electro-conductivity of a fluid being an index of its inner friction. Although some years ago Starling, and other observers later, showed that colloids have, or may have, some slight electro-conductivity, yet, generally speaking, they are non-conductors, and their inner friction is high; without the impulses of saline ingredients they are almost non-osmotic, and it is by this virtue of its colloids that the blood is protected against the continual fluctuations in the densities of its saline constituents. Still, as we have seen, while some electrolytes lower the viscosity of colloids, others raise it.

Now, passing from the blood itself, we come to consider the relations of this complex fluid to the multiform cells of the body, for between these and the fluids, as Waymouth Reid and others have shown, there is an incessant play of specific alternating phases, according to the wide differences in specific endowment of the cells, differences which, for lack of a better word, we may call vital; differences at any rate of internal structure whereby they exercise remarkable selective functions, so that only certain kinds of reciprocation, or physiological permeability (6), can take place in each area; the kidneys selecting some ingredients, the pancreas others, the gastro-intestinal canal others, and so forth. A most striking example of these 'vital' peculiarities is the acquired osmotic impermeability, for obvious purposes, of the healthy epithelium of the bladder *in situ*; a protective property which fails when the coat is injured or de-

teriorated.<sup>9</sup> So to remove the living epithelium from the intestine makes absorption not easier but more difficult. Again, in like manner it is not easy on physico-chemical grounds to understand the transfer, by the renal membranes, of the urea from the blood, in which the urea is in very low dilution, to the urine, in which its proportion is high; or again, their refusal of sugar, which is far more abundant in the blood than urea. Another physiological idiosyncrasy we shall note presently in the red blood-cells. The specific build and reaction of the sundry tissue cells, the peculiar and complementary function of each, and the consequent various but in its concert complete and harmonious play with the aggregate of the many foods and the mutual phases of the nutritive juices give us a notion, however inadequate, of the enormous power which these physico-chemical, and apparently also peculiarly physiological, processes incessantly at work in the body must exert even under small changes of salt content; a notion likewise of the equilibrium so perfect in its evolution that in spite of the variety of cell-structure and operation, of changing blood content, in spite of the strife of opposing tensions, of the calls of the hormones, of the interventions of the nervous system, of the affairs of the whole body engaged in its world, the oscillations in health are so small, and so perpetually balanced, as to maintain not only stability but a practical equilibrium; such an equilibrium, indeed, as to baffle the investigator in his endeavour to record them. Thus throughout this vast area of surface and field of reciprocal function there is a practical isosmosis and isoviscosity; although on the balance we must presume a slight proclivity of osmotic pressure from tissues to blood in its mean between arterial and venous; and that the lymph on the balance must be slightly less viscous—less colloid—than the blood.

And as with these solids and fluids as wholes, so with their parts; as between the corporeal cells and fluids, so between the blood corpuscles and the plasma, a continual osmotic (and ultra-physical?) reciprocation is in play. Among their other endowments the blood corpuscles play a considerable part in the balances and reserves of the whole blood. Being permeable to some inorganic ions and not to others, under these influences they change in form—swell or shrink—according to the swings of plasmatic constituents; so that on account of its corpuscles the viscosity of the whole blood varies more than that of the plasma. We have seen that much of the viscosity depends on the haemoglobin and gas content (1); on the addition of  $\text{CO}_2$  the chlor-ions penetrate from the plasma into the corpuscles, so that their watery content increases, and the molecular concentration of the plasma increases. Sodium chloride is a most active ionizing and osmotic agent in the plasma. The plasma is more electro-conductive, the corpuscles are more colloid, and, as already stated, are permeable to some salts, not permeable to others. At present it would seem that by an ultra-physical—by some more complex biological ('vital')—endowment of the

<sup>9</sup> Upon the function of lipoids as investments of or clews amid the molecules I have not touched, as I see the experts are not as yet in substantial agreement on this subject.

corpuscular edge or 'membrane' the inorganic constituents of the cells and the plasma stand various and unequal; the corpuscle being rich in potassium and phosphate, the plasma in sodium and chloride (6). It is at this boundary, in its origin almost ideal, that we note the initiation of inhibition, the fundamental character of organized life, of survival by an economic faculty preventing dissipation of energy, and storing it for larger and farther ends. For this auto-limitation, viscosity and friction, by retarding physico-chemical processes, give the conditions.<sup>10</sup> And it is here that for a moment we may glance again towards one of the most practical problems of the clinical physician, at the resources of the body, its reserves, or potential. In advancing years we suspect that the tissues become less permeable; osmosis is less active, less free; but to equalize the rises and falls of viscosity, or osmotic tension, the cells must be readily pervious to water. For example, in laboratory experiments with yeast, the cells must be fresh, 'hatched' within an hour or two; cells of the day before are far less sensitive.

It has been said that for reserve or discharge the secretions and excretions by their fluidity or visciduity play a large part in equalizing viscosity; of these the part of the urine must be important, if not the chief; to the urine, therefore, no little attention has been given, and much help was anticipated by v. Korányi and others from *cryoscopy* in estimating these exchanges. Unfortunately, Rose Bradford,<sup>11</sup> Sir James Barr, in private letter, Sahli,<sup>12</sup> Winternitz,<sup>13</sup> and other careful observers have found its indications, which of course fluctuate largely in health, unavailable, at any rate in this respect; as likewise with those of electro-conductivity. It tells us no more than the concentration at the moment of the dissolved substances, and we get no more out of it than out of specific gravity. To weigh the ashes of a locomotive does not go far in a computation of its efficiency. For instance, if the kidneys fail to carry off the waste products the molecular concentration of the blood, and therefore its freezing-point, should rise, and its electro-conductivity fall; but other variables are such that even in uraemia this is not regularly the case; and cryoscopy of the urine, and conversely of the blood, fails to tell whether after operation on one kidney the other is healthy or not. To test the concentration of the blood, and so indirectly the renal efficiency, by cryoscopy needs a venesection of 20 cm. And it seems to me that even then it would be impossible to exclude falls of concentration due to variations of cardiac energy or other causes of rising venous pressures. If electro-conductivity should fall independently of the freezing-point it would suggest a retention of organic molecules. A little proteid, however toxic, would scarcely alter the freezing-point. The freezing-points of the whole blood and of the plasma are practically identical; suspended particles make no difference,

<sup>10</sup> For an interesting study of these phases, see F. H. Garrison, 'Physiology and the Second Law of Thermo-dynamics,' *New York Med. Journal*, Sept. 25, 1900.

<sup>11</sup> Allbutt and Rolleston, *System of Medicine*, edit. 2, iv, pt. i, 535.

<sup>12</sup> *Klin. Methoden*, edit. 5, 1909, ii. 748. Sahli criticizes v. Korányi's methods as fallacious.

<sup>13</sup> In Krause's *Lehrbuch*, 1909, 259-60.

quartz dust for instance suspended in a similar solution makes no difference; but the conductivity on the contrary of the whole blood is but half that of the serum from which the corpuscles, which obstruct conduction, have been removed.

On the sum of such data as these which we have been considering Du Pre, Denning, and Watson (16) formed the provisional opinion that viscosity seemed to be not an independent but a dependent variable; one not dominant in the circulation but by its adaptive changes contributory to the maintenance of its consistency and efficiency. At present, indeed, it is not clear from what has gone before that in pathological states its adaptations are beneficial always; but with so much that is obscure or even contradictory in the evidence we must for the present hold our judgement in suspense. From these inconclusive data and still speculative notions, vitally important as the facts may be, and enlarging as these concepts are to our physiological vision, it must be admitted that no principles can as yet be formulated for application to practical medicine. Although, as Hess says (20), (other things being equal) a stickier blood must increase the burden of the heart on both sides, yet it is true that this variable quality may be met by so many readjustments as to be virtually a constant. If a thicker blood flow more slowly water will soon gather in the body; if a thinner and less valuable blood flow more rapidly the urinary effluent will soon be increased, and the normal viscosity restored. Yet a thinner blood, if, as is probable, it be in larger mass, and if, as less nutritious per unit, it be run at greater speed, and such with equal aortic pressure would be the case, the heart would be no less burdened; though not necessarily with any rise of blood-pressure. It is said that injection of gelatin into a vein produces no rise of blood-pressure. I am still disposed to think that a superviscous blood may be concerned in some modes of arterial strain.

Further research on this subject will lead, I believe, to some clinical and therapeutical results. For there is some evidence that in abnormal states these readjustments, in health so ready, in disorder may lag; it is alleged, for instance, that in the state of excessive blood-pressure described independently by Huchard and by myself in 1893-4 as precursory of arterio-sclerosis, and named by me Hyperpiesis, by Huchard Presclerosis, the viscosity of the blood is, or may be, raised; the observations on this point are however as yet too few and too lacking in authority to establish a rule. The difficulty of attaining to exact knowledge in this matter is illustrated by the uncertainty which in these respects still surrounds the effects of iodide of potassium upon the arterial circulation. We have noted how tenaciously, in spite of the lack of definite evidence of its mode of action, clinical practitioners cling to the prescription of this salt in 'arterio-sclerosis'; and this in justifiable disregard of pharmacological opinions—justifiable, that is, if it appears to them that the clinical effects are decisively in its favour. Yet so far as experiment upon normal men and animals has gone, little evidence of the effect of moderate doses of iodide of potassium in reducing viscosity of the blood has been obtained. Ottfried Müller and Inada, (30) whose

researches were carried out under Romberg's supervision (Hirsch and Beck's instrument), found that the iodide had a 'favourable effect upon arterio-sclerosis', (33) not by any effect upon the vessels but upon the blood viscosity, which in 9 out of 11 men was reduced in degrees from 1.7 to 8.3 per cent. They stated, moreover, that they had demonstrated a gain of four seconds in stream velocity. But on the other hand Adam, (1) who administered potassium iodide in full doses—i.e. 45 grains a day—found a reduction of viscosity in only 6 of 30, and that doses of 20–30 grains made no difference at all; Determann likewise has been unable to detect any reduction of viscosity under the salt. *In vitro* it is well known that iodide of potassium reduces viscosity in watery solutions of serum-albumin, and in blood plasma; and we have recognized the large effect which a relatively small reduction would have on the whole blood. The conflict of evidence as to the effect of the iodides may be due in part to a time difference; or possibly to an alleged effect of potassium salts, when injected into a vein, of constricting the arterioles. This property, if such it be, appears not to have been taken into consideration. In the discussion at the Wiesbaden Congress (1909) to which I have referred, Umber of Altona said that in his wards Jorns, in a long series of cases, had noted reductions of viscosity on administration of the iodides in no very large doses but over long periods of time. Boveri (8) administered iodine compounds to twelve persons with 'hypertension', some with and some without arterio-sclerosis, and tested the whole blood, and the serum, at intervals of 10, 20, 30, 40 days. In eight of the cases there was a fall of viscosity from 10 per cent. downwards. The differences are not large, and (in my summary, at any rate) the hours of the day on each examination are not mentioned. On the whole Boveri says there seems to be a parallelism between arterio-sclerosis—presumably that consequent upon the 'hypertension'—and the viscosity of the blood, and (contrariwise) iodine ingestion. But it is to be observed that these falls were in the whole blood, the serum in all the cases being recorded as stationary; the effect, therefore—if the effect were substantial—was in the proportionate number of corpuscles, or the quantity of haemoglobin. It has been suggested that a comparison of the blood of Graves's disease and of myxoedema, and again of the blood before and after thyroid operation, might throw some light on the iodine charges. A few experiments upon animals by Burton-Opitz and others seem to indicate some pathological fluctuations of this kind.

Mineral waters, as affecting blood viscosity, have received some attention, and are credited with some power of reducing it. This effect seems to have been noted chiefly in those big feeders and plethorics who frequent such resorts, and whose blood, as we have seen, is alleged to be overviscous. If this prove to be true, both as to the hyperviscosity and the relief of it, we shall have gained a very useful indication for scientific treatment.

In the study of the effects of baths a few investigations have been made by Determann and others. In these external applications of air, water, light, &c., the action of the vasomotor system and the partial distributions of the



Now, as the fine vessels of the lungs are of comparatively constant radius, excessive internal friction must tell more immediately on them. We are little able to measure this effect directly, but in practice we meet daily with cases of gradually encroaching cyanosis, due primarily to bronchial, emphysematous, or more general causes, which lead to or are associated with dilatation of the right side of the heart. It seems probable that in these cases, as in other multiples of cyanosis, among many co-operative factors, increments of viscosity may play no inconsiderable part.

## REFERENCES.

1. Adam, *Zeitschr. f. klin. Med.*, Berlin, 1909, lxxviii. 177.
2. Asher and Spiro, *Ergeb. d. Physiol.*, 1907, vi (quoted by Krone in a useful essay in the *Deutsch. med. Woch.*, 1910, xxxvi. 1438).
3. Baehmann, *Deutsch. Arch. f. klin. Med.*, 1908, xciv. 409.
4. Beck and Hirsch, *Arch. f. exper. Path. und Pharmacol.*, 1906, liv. 54.
5. Blunschy, quoted by Krone and by Determann.
6. Boruttau, *Med. Physik*, 1908; Philip, *Physical Chemistry*, 1910, and other authors on this subject. The observations of Barcroft and Orbeli (*Journ. of Physiol.*, Jan., 1911) on the effect of lactic acid, also in sweeping out low-tension oxygen from the tissues, are very interesting.
7. Botazzi, *Biochem. Zeitschr.*, 1908, vii, quoted by Determann.
8. Boveri, 'Viscosité du sang et iode,' *La Presse méd.*, 1908; extracted in *Arch. d. mal. du cœur*, 1909, 255.
9. Bruce and Alexander, *Journ. Mental Sci.*, Lond., 1890, xli. 725.
10. Burton-Opitz, *Stud. Rockefeller Inst. Med. Research*, vi. 190; and Hirsch and Beck, *Deutsch. Arch. f. klin. Med.*, 1900-1, lxi. 503.
11. Burton-Opitz, *Stud. Rockefeller Inst. Med. Res.*, 1907, vi. 190.
12. Burton-Opitz, *Journ. Physiol.*, Camb., U.S.A., 1905, xxxii. 8.
13. Determann, *Die Viskosität des menschlichen Blutes*, Wiesbaden, 1910. Its usefulness is impaired by the lack of indexes.
14. Determann, *Zeitschr. f. klin. Med.*, Berlin, 1909, lxxviii. 177.
15. Determann, loc. cit. (13); and Hess, *Münch. med. Wochenschr.*, 1907. The gas content of various bloods was estimated on Barcroft's method.
16. Du Prc, Denning, and Watson, *Proc. Royal Soc.*, Oct. 24, 1900; and No. 78, 1906.
17. Erb, *Deutsch. Arch. f. klin. Med.*, 1907.
18. Hasebroek, reported in *Deutsch. med. Woch.*, 1909, xxxv. 1414.
19. Hess (Walter, of Zurich), *Deutsch. Arch. f. klin. Med.*, 1903-4, lxxix. 128; and (on instruments) *Münch. med. Wochenschr.*, 1907, liv. 2. 1590; also in collaboration with Determann; and 'Die Viskosität des Blutes bei Gesunden,' *Deutsch. Arch. f. klin. Med.*, 1908, xciv.
20. Hess, *Deutsch. Arch. f. klin. Med.*, 1908, xciv. 404.
21. Hess, *Deutsch. Arch. f. klin. Med.*, 1908-9, cxv. 482.
22. See Hess, 'Viskosität d. Blutes und Herzarbeit,' *Vierteljahrsschr. d. Naturf.-Ges. in Zürich*, 1906.
23. Hirsch and Beck, loc. cit. (4).
24. Hürthle, *Pflüger's Arch. f. ges. Physiol.*, Bonn, 1900, lxxxii. 438.
25. Hutchinson and Miller, *Lancet*, Lond., 1906, i. 744.
26. Kündig, *Diss.*, Jena, 1903, quoted by Krone.
27. Lommel, *Deutsch. Arch. f. klin. Med.*, 1904, lxxx. 308 (quoted by Krone); and *Münch. med. Wochenschr.*, 1908, No. 6 (quoted by Determann, loc. cit.).

28. McCaskey, *Journ. Amer. Med. Assoc.*, Chicago, 1908, li. 1653 (quoted by Krone).
29. Mott, *Phil. Trans.*, Lond., 1899, Ser. B, cxi. 211.
30. Müller (Ottfried) and Inada, *Deutsch. med. Woch.*, 1904, xxx. 1751; and *Ther. d. Gegenwart*, 1906, 360-361; see also the reports of the *Kongr. f. inn. Med.*, Wiesbaden, 1909.
31. Pauli, *Kolloidchemische Studien an Eiweiss*, Dresden, 1908; and *Kolloidchemische Zeitschr.*, Bd. 3. (I have not seen either of these, but they are freely quoted in other essays and handbooks; e. g. Philip, *Physical Chemistry*, 1910; Determann, loc. cit., &c.)
32. Ribaudi, quoted in *Arch. d. mal. du cœur*, 1909, 256.
33. Romberg, *Lehrbuch d. Herzkrankheiten*; who upon this recommends iodide of potassium in coronary sclerosis.
34. Tigerstedt, quoted by Krone, *Deutsch. med. Woch.*, 1910, xxxvi. 1438.
35. Turner, Dawson, *Nature*, Lond., 1902, lxi. 127.
36. Turner, Dawson, *Proc. Royal Soc. Edin.*, 1891-92, xix. 20, quoted by himself, *Nature*, 1902, lxi. 127.
37. Weber, Parkes, the first case, *Lancet*, Lond., 1905, i. 1254; the second case, Parkes Weber and Dorner, *Lancet*, 1911.

# THE INFLUENCE OF BACTERIAL EMULSIONS ON PHAGOCYTOSIS

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THE effect of the presence of bacterial emulsions on the phagocytic power of leucocytes does not appear to have received much attention. It is, however, obvious that the opsonic theory rests upon the tacit assumption that the presence of bacteria in an emulsion containing leucocytes does not in itself affect the phagocytic activity of the leucocyte.

This paper contains an attempt to estimate the effect of bacteria on phagocytosis, and it is claimed that the results obtained are such as to make the theory of opsonins untenable.

*Technique.* To measure the phagocytic activity it was necessary to select as a food-stuff some substance that could not be chemically altered and that was incapable of physically absorbing the supposed opsonic bodies. For this purpose fragments of charcoal or the particles of melanin used by Dudgeon in his experiments on phagocytosis are obviously inadmissible. After some experiments with rouge and various fine chemical precipitates, carborundum was finally selected. This substance can be readily obtained in the shape of small glistening crystals with an average cross-section of about five to eight  $\mu$ . They can be very readily detected as brilliant refractile bodies in the cell, and practically no difficulties can arise in the enumeration when a not too thick emulsion is used. In all the experiments very much larger quantities of material were used than are adopted in the routine performance of opsonic counts. 0.1 c.c. of serum was mixed with equal volumes of a white cell suspension and an emulsion of carborundum in normal saline. Tap-water was always used for the normal saline solution: pure sodium chloride in distilled water is toxic to the leucocytes, and the phagocytosis is much less than when tap-water saline is used. When bacterial emulsions were employed, the serum was treated with an equal volume of these suspended in normal saline. The mixtures were always intimately mixed by blowing bubbles of air through them before being sucked up into Widal pipettes for incubation. This is a very necessary measure, as the carborundum particles readily tend to subside at the bottom of the mixture. In order to ensure uniform distribution of the carborundum during incubation the sealed Widal pipettes were inserted in compartments of a wheel driven by a clockwork motor revolving four times a minute. Incubation was carried on at 37° C. for about half an hour, and at the end of this

period the tubes were removed, and their contents were blown out on large slides, fixed in formalin and stained with carbol thionin. No attempt was made to secure a conglomeration of the leucocytes at the edge of the film, as it was found that the accuracy of the counts was very considerably enhanced when the leucocytes were distributed over thin and even films, although the labour of counting was of course very greatly increased. Leucocytes do not so readily take up the large and heavy carborundum particles as they do the small and light bacteria, and the number of cells containing carborundum crystals is seldom, even after an hour's incubation, greater than 80 per cent. of the total number of cells. This statement would of course be capable of modification by any one using a more finely divided carborundum than that which I found to be convenient. In my preparations only a small minority of the carborundum-containing cells had more than one contained crystal, and phagocytic activity was therefore measured by estimating the number of cells which had taken up carborundum, and not, as in the opsonic method, by the mean number of particles absorbed per cell. It is obvious that for such a method to give accurate results a very large number of cells must be counted, as against the standard sixty leucocytes of opsonic determinations, and it was the rule to count 500 cells in each slide. As the experiments were always done in duplicate, a comparison of two sera involved the counting of a minimum of 2,000 cells, and often more than one slide for each preparation was made. An analysis of counts with good clean films shows that the mean error of counting is not above 2 per cent., and in a number of comparisons of different preparations made from the same sera and emulsions it was found that the mean error in such comparisons was about 5 per cent., though with good preparations it was of course considerably less.

*The influence of bacteria on phagocytosis in normal saline.* Hamburger has shown that phagocytosis of charcoal particles occurs readily in normal saline, and by this method has measured the effects on phagocytic activity of solutions of different concentrations. The phagocytosis of carborundum particles in normal saline, however, is slight, and this method is not adapted for demonstrating readily the inhibitory action of bacteria on phagocytosis. In the trials made, however, such an inhibitory influence could be clearly seen.

*Experiment.* To a volume of washed corpuscles in 6 per cent. sodium chloride an equal volume of a suspension of washed bacteria in saline solution of the same strength was added. A control preparation of cells and an equal volume of plain normal saline were made. To each preparation an equal volume of a suspension of carborundum in normal saline was added and the preparations were incubated in Widal tubes for thirty-five minutes.

Normal saline, cells, carborundum. Phagocytic index = 1.

Tubercle emulsion, cells, carborundum. P. index = 0.32.

Staphylococci emulsion, cells, carborundum. P. index = 0.3.

Typhoid emulsion, cells, carborundum. P. index = 0.43.

Diphtheria emulsion, cells, carborundum. P. index = 0.81.

The phagocytosis of carborundum crystals in the presence of normal serum

is far greater than that in saline solutions, though owing to the protection afforded by the serum to the leucocytes, proofs of which will be given later, the diminution of phagocytic activity due to the presence of bacteria is less marked.

The following experiments are given from a very large number, in all of which the inhibitory action of different bacterial emulsions on phagocytosis could be shown.

(a) Equal volumes of serum, normal saline. Carborundum emulsion gave phagocytic index of = 1.

Substitution of emulsion of *Staphylococcus aureus* for normal saline. Phagocytic index = 0.7.

Same experiment but with bacillary emulsion double strength. P. index = 0.4.

(b) Tubercle emulsion substituted for normal saline. P. index = 0.8.

Same experiment but double strength of tubercle emulsion. P. index = 0.7.

(c) Emulsion of *Bacillus typhosus* substituted for normal saline. P. index = 0.6.

Similar inhibition of phagocytosis was verified for *B. coli*, *Pneumococcus pneumoniae*, *B. diphtheria*, and *Streptococcus pyogenes*.

*The protective action of the serum against the anti-phagocytic effect of bacterial emulsions.* Carborundum phagocytosis is markedly diminished when serum heated for fifteen minutes at 60°C. is substituted for normal serum. In bacteriological parlance this would be said to be due to destruction of 'stimulins' at that temperature. The changes that have been observed in surface tension in heated serum would lead one to suspect that the explanation may be expressed in more precise physical terms. If the diminution of phagocytosis of carborundum be compared when two cell and normal saline preparations are severally incubated with unheated and heated serum, and again when two cell and bacterial emulsion preparations are similarly incubated with heated and unheated serum, it will be found that the phagocytic index is proportionately more reduced in the bacterial preparations than in those made with normal saline. Thus:—

Equal parts of cell emulsion, fresh serum, and normal saline, incubated with carborundum. Phagocytosis = 15 per cent. P. index = 1.

Equal parts of cells, tubercle emulsion, and fresh serum, incubated with carborundum. P. = 9 per cent. P. index = 0.6.

Equal parts of cells, heated serum, and normal saline, incubated with carborundum. P. = 7.6 per cent. P. index = 1.

Equal parts of cells, heated serum, and tubercle emulsion, incubated with carborundum. P. = 4.1 per cent. P. index = 0.53.

The protective body in the serum combines with the bacteria. If bacteria are treated with normal serum and then washed free from serum, and then suspended in normal saline and mixed with equal volumes of a cell carborundum emulsion, it will be found that a much greater carborundum phagocytosis takes place than in the presence of an equal quantity of bacteria which have not been subjected to the action of serum. Inasmuch as more of the treated bacteria are taken up by the leucocytes, this experiment incidentally furnishes an answer to

an objection that might have been suggested by the earlier experiments quoted—that the phagocytosis of bacteria might mechanically impair the phagocytosis of carborundum.

The protective body of normal serum is not present in heated serum, but when bound to the bacilli it cannot be displaced by heating. Equal volumes of bacterial emulsions were treated with normal and heated serum respectively: after fifteen minutes' incubation the serum was washed off and the washed bacteria suspended in equal volumes of normal saline. The suspensions were heated to 64° C. for fifteen minutes and then incubated with equal volumes of cell emulsion and normal saline.

(a) Tubercular emulsion treated with normal serum, washed, heated, and incubated with cell carborundum emulsion. Phagocytosis = 52 per cent. Tubercle emulsion treated with heated serum, washed, heated, and incubated with cell carborundum emulsion. P. = 37 per cent.

(b) B. Gaertner bacillus was treated with heated and unheated serum in the same way as in the above experiment. Three separate preparations were made with heated and unheated serum respectively. In this case the serum was that of an immunized rabbit, rich in antitoxin to B. Gaertner, given me by Dr. Slater.

Three Gaertner emulsions treated with unheated immune serum, washed and heated and incubated with equal volumes of cell carborundum emulsions. P. respectively = 24, 24, and 20 per cent.

B. Gaertner emulsion treated with heated immune serum, washed, heated, and incubated with equal volumes of cell carborundum emulsion. P. = 19, 17, 17.2 per cent. respectively.

B. diphtheria was similarly treated with heated and unheated serum. Fresh antidiphtheritic horse serum was used.

Two portions of emulsion of B. diphtheria treated with fresh immune serum, washed, heated, and incubated with cell carborundum emulsion. P. = 75 and 79 per cent. respectively.

(c) Two emulsions of B. diphtheria treated with heated immune serum, washed, and heated. Incubated with cell carborundum emulsion. P. = 47 and 48 per cent. respectively.

A more convenient and accurate method was found to be that of allowing the serum to remain during the incubation. Thus:—A volume of bacterial emulsion was treated with normal serum, incubated for fifteen minutes at 37° C. and the mixture eventually heated for fifteen minutes at 64° C. An equal volume of emulsion was heated for fifteen minutes at 64° C. and incubated for another fifteen minutes at 37° C. together with an equal volume of serum which had also been previously heated at 64° C. for fifteen minutes. The two prepared emulsions were now incubated with a cell carborundum mixture.

(a) Two portions of tubercle emulsion treated as described with previously unheated serum and incubated with cell carborundum emulsion gave phagocytosis of 61 and 63 per cent. respectively.

Two emulsions of tubercle treated with previously heated serum and incubated with cell carborundum emulsion gave phagocytosis of 43 and 44.5 per cent. respectively.

(b) *Staphylococcus aureus* emulsion treated with previously unheated serum as described. P. = 65 per cent.

*Staphylococcus aureus* treated with previously heated serum. P. = 45 per cent.

(c) Diphtheria emulsion treated with previously unheated serum as described. P. = 45 per cent.

Diphtheria emulsion treated with previously heated serum. P. = 35 per cent.

Equal volumes of normal saline treated with heated and unheated serum in same fashion as diphtheritic emulsions gave phagocytosis 51 and 49 per cent. respectively.

These experiments have been confirmed by a number of others using the same micro-organisms.

The antiphagocytic action of bacteria depends upon their bodily presence in the fluid containing the phagocyte, and on incubation with serum they do not give off any antiphagocytic substance to the serum. Numerous experiments with various micro-organisms have been conducted in order to elucidate this point. Emulsions of bacteria were incubated with serum and, after a varying length of time, centrifugalized off. Serum so treated had no inhibitory action on phagocytosis when compared with equal volumes of serum treated with normal saline instead of bacterial emulsion. It appears to be unnecessary, therefore, to give a list of the negative results that have been invariably obtained.

The substance of normal serum combining with the bacteria and neutralizing their antiphagocytic power is not specific. It has already been shown that the neutralizing substance of normal serum combines with the bacteria in such a fashion that it cannot be washed away and the resulting combination is resistant to the action of heat. In order to find out whether this body combining with different micro-organisms was the same in every case, numerous experiments were performed in which normal serum was allowed to act on bacterial emulsions, and after the micro-organisms had been centrifugalized off, emulsions of the same or different bacteria were added to the serum and the effect on the phagocytosis of carborundum noted. A few of the experiments performed are recorded below.

Five equal volumes of normal serum were taken. Sera A, B, and C were incubated for fifteen minutes with equal volumes of normal saline. Sera D and E were incubated with an equal volume of typhoid emulsion for fifteen minutes. Sera D and E were then centrifugalized and from each of the five sera an equal volume was withdrawn and placed in separate capsules. To capsule A was added an equal volume of normal saline, to capsule B an equal volume of typhoid emulsion, to capsule C an equal volume of tubercle emulsion, to capsule D an equal volume of typhoid emulsion, and to capsule E an equal volume of tubercle emulsion. To each capsule equal volumes of leucocytic and carborundum emulsions were now added, portions from each capsule were

drawn off in Widal pipettes, incubated for thirty-five minutes, and films made. The phagocytosis was found to be as follows :—

- A. Saline, serum and saline. Phagocytosis = 50.5 per cent.
- B. Saline, serum and typhoid emulsion. P. = 43.5 per cent.
- C. Saline, serum and tubercle emulsion. P. = 35 per cent.
- D. Emulsion of typhoid (centrifugalized), serum, tubercle emulsion. P. = 26 per cent.
- E. Emulsion of typhoid (centrifugalized), serum, typhoid emulsion. P. = 35 per cent.

It will be seen that in this experiment, deducing the inhibitory power of the tubercle emulsion as 15 by subtracting result C from result A, and assigning to the typhoid emulsion an inhibitory value of 7 by subtracting result B from result A, we should then expect to find the inhibition values of the typhoid tubercle, preparation D, to be equal to  $15 + 7 = 22$ , and in practice the value obtained is 24.5. The inhibitory value of the typhoid, typhoid preparation E, should be  $7 + 7 = 14$ , and in practice we find 15. This experiment furnishes conclusive evidence that the body neutralizing the antiphagocytic power of bacteria is not specific as regards typhoid and tubercle.

Another experiment with *Staphylococcus aureus* and tubercle may be quoted, the procedure being the same as in the experiment above described.

- A. Saline, serum, saline. Phagocytosis = 43 per cent.
- B. *Staphylococcus* emulsion (centrifugalized), serum, tubercle emulsion. P. = 30 per cent.
- C. *Staphylococcus* emulsion (centrifugalized), serum, *staphylococcus* emulsion. P. = 20 per cent.
- D. Tubercle emulsion (centrifugalized), serum, *staphylococcus* emulsion. P. = 31 per cent.
- E. Tubercle emulsion (centrifugalized), serum, tubercle emulsion. P. = 36 per cent.
- F. Saline, serum and tubercle emulsion. P. = 39 per cent.
- G. Saline, serum, *staphylococcus* emulsion. Film damaged through accident.

Similar results were obtained with emulsions of *staphylococcus* and typhoid and with tubercle and *streptococcus*. In all cases no evidence of any specificity of the neutralizing power of normal serum on the antiphagocytic action of bacteria could be obtained.

The neutralizing power of normal serum on the antiphagocytic action of micro-organisms is the same in any two or more normal serums for any definite micro-organism. The truth of this statement has been proved by numerous experiments. As, however, working with the relatively large amounts of serum used, it is difficult to obtain sufficient leucocytes to investigate more than six sets of sera at a time, the groups of experiments have had to be numerous and do not lend themselves to exposition within the limits of a short paper.

In sera taken from pathological cases, the neutralizing power of the serum



may differ from that of normal serum with regard to the specific organism causing the disease in any one case. Further variations of neutralizing power may be brought about in pathological sera by vaccination with the specific micro-organism, and such variations may be shown to agree with similar variations observed in the opsonic index. In proof of these statements a series of isolated observations on cases of disease and some continuous ones on the effect of inoculation are appended. Where opsonic determinations have been made, these are added. In all cases the amount of phagocytosis is expressed in terms of the phagocytosis with normal serum, which is taken as unity. The opsonic indices were kindly done for me by Dr. Hunt of the St. George's Hospital bacteriological department. In all cases when two or more sera were compared the leucocytic emulsion was made from the cells of a third normal subject. It must be remembered that, as the periods of incubation in the opsonic and in the carborundum phagocytosis experiments are purely arbitrary and bear no necessary relation to the optimum period of time for showing the maximum difference in either case, the results can only be expected to show a variation in the same direction, and it will be seen that they do so with a far greater frequency than could be expected were the relation purely one of coincidence.

- (1) Tuberculous woman (slight pulmonary affection). P. index = 0.84.  
Opsonic index = 0.9.
- (2) Woman (tuberculous shoulder). P. index = 1.37. Opsonic index = 1.25.
- (3) Woman (bad case of phthisis). P. index = 0.97. Opsonic index = 0.98.
- (4) Man (recovering from malignant endocarditis). Own bacteria used for emulsion. P. index = 0.85. Opsonic index = 0.9.
- (5) Tuberculous man. Phthisis (losing ground). Compared with mean of three normal sera. P. index = 0.58.
- (6) Man. Staphylococcal infection (convalescent). P. index = 2.5. Opsonic index = 2.0.
- (7) Tuberculous woman (phthisis). Before and 48 hours after injection of 0.001 mg. O. T.  
Before—P. index = 0.9. Opsonic index = 2.0.  
After—P. index = 1.3. Opsonic index = 2.3.
- (8) Rabbit immunized with typhoid and agglutinating typhoid bacteria strongly, had been kept for a year for Widal reactions. P. index against normal rabbit (cells of third rabbit used) = 1.7.
- (9) Case of phthisis. Before and 48 hours after injection of 0.001 O. T.  
Before—P. index = 1. Opsonic index = 1.4.  
After—P. index = 2. Opsonic index = 2.3.
- (10) Young man with aene. Pure staphylococcus cultivated from pustules from which a vaccine was prepared. Before and 48 hours after vaccination of 300,000,000 cocci.  
Before—P. index = 1.1.  
After—P. index = 0.7.

- (11) Case of pneumonia, 48 hours after crisis. P. index = 1.3.  
 (12) Case of pneumonia, 8 days after crisis. P. index = 1.  
 (13) Young man suffering from acne. *Staphylococcus griseus* alone cultivated from pustules. Vaccine prepared. Also emulsions for opsonic and phagocytic determinations.  
 Jan. 9, 1911. P. index = 1.15. Opsonic index = 1.05. Injection of 100,000,000 cocci given.  
 Jan. 10. 24 hours after injection. P. index = 0.5. Opsonic index = 0.85.  
 Jan. 13. 72 hours after injection. P. index = 0.95. Opsonic index = 0.85.  
 Jan. 16. P. index = 0.97. Opsonic index = 0.95. Injection of 200,000,000 cocci.  
 Jan. 17. 24 hours after injection. P. index = 0.85. Opsonic index = 1.25.  
 Jan. 19. 72 hours after injection. P. index not taken. Opsonic index = 1.35.  
 Jan. 23. P. index = 1.1. Opsonic index = 1. Injection of 500,000,000 cocci given.  
 Jan. 24. 24 hours after injection. P. index = 0.3. Opsonic index = 0.65.  
 Jan. 26. P. index = 0.9. Opsonic index = 0.95.

(14) Case of typhoid (two weeks after defervescence). P. index = 1.3.

The above list of cases includes all those done with pathological material.

A pathological rise of the phagocytic index appears to be specific. That is, the neutralizing power of the serum towards the antiphagocytic action of bacteria is heightened only for the bacteria which have caused the specific malady from which the patient suffers. When the neutralizing power of the serum is lowered, this lowering does not appear to be specific, but the phagocytic index is lowered to other non-specific bacteria. If this assertion can be justified it would appear that when the phagocytic index is raised, a new specific neutralizing body differing from the non-specific body of normal serum has made its appearance. A lowering of the phagocytic index on the other hand implies a diminution in the amount or potency of the non-specific neutralizing substance present in normal serum. It must be admitted that these assertions rest on slender evidence, as up to the present only four experiments have been performed.

(a) Serum of a man recovering from staphylococcic infection gave a phagocytic index of 2.5 with emulsion of his own cocci.

Same serum gave with an emulsion of tubercle bacilli an index of 1.

(b) Serum of pneumonia case, 48 hours after crisis, gave to pneumococcus emulsion P. index = 1.4.

Same serum with tubercle emulsion gave index of 1.1.

(c) Serum of acne case after vaccination gave to emulsion of own cocci P. index = 0.3.

Same case with an emulsion of *B. coli* gave P. index = .56.

Case of tuberculosis gave with tubercle emulsion P. index = 0.84.

Same serum with pneumococcus emulsion gave P. index = 0.9.

The results of the experiments given in this paper tend to show that a much simpler explanation can be given of the opsonic phenomenon than that generally accepted. Bacterial emulsions have been shown to have a decidedly inhibitory influence on the phagocytic activity of leucocytes, normal serum has been shown to have the power of protecting the leucocytes against this anti-phagocytic influence. Heated serum appears to have no protective power on phagocytosis in the presence of bacteria. The protective substance forms a thermostable combination with bacteria. The protective substance of normal serum is not specific, and the same absence of specificity has been shown by the experiments of York and Smith, in contradiction of the earlier work of Bulloch and Western, to be true of the so-called opsonins.

Pathological variations in the phagocytic index have been shown to correspond roughly with the opsonic index, and such variations in both indices may be caused by vaccination with the appropriate micro-organism.

There is some evidence that the excess of protective substance in sera giving a high phagocytic index is specific to the micro-organism with which such a high index is associated, and the same statement has generally been made of the opsonic index.

It would appear, therefore, that the cause of variation in the phagocytosis of the chemically inactive carborundum crystals and of bacteria in the presence of bacterial emulsions must therefore be assigned to one and the same cause, that is, to variations in the protective power of the serum for leucocytes against the toxic antiphagocytic action of bacterial emulsions which are present in both cases. The correspondence between the two methods of estimation, carborundum and bacterial phagocytosis, would be more striking were it not for the fact that the heavy carborundum particles are capable of being ingested in the presence of neutral or unfavourable media, such as normal saline and heated serum, whilst the lighter and smaller bacteria escape ingestion, and secondly, that owing to the large-sized particles used the smaller leucocytes do not as a rule exhibit carborundum phagocytosis, hence there is always a considerable number of empty cells in a carborundum phagocytic count under conditions in which practically every leucocyte would have ingested bacteria to its full capacity. This difference would probably disappear were smaller particles of carborundum adopted and counts of the percentage of ingested granules per cell made.

In conclusion, I have to thank Dr. Slater, Director of the St. George's Hospital bacteriological laboratory, for his kindness in providing me with material, and Dr. Hunt for having performed numerous opsonic determinations.

#### REFERENCES.

- Bulloch and Western, *Proc. Roy. Soc., Lond.*, 1906, B. lxxvii. 531.  
Hamburger und de Haan, *Biochem. Zeitschr.*, Berlin, 1910, xxiv. 304.  
Shattock and Dudgeon, *Proc. Roy. Soc., Lond.*, 1908, B. lxxx. 165.  
York and Smith, *Biochem. Journ.*, Liverpool, 1907, ii. 76.

# TUBERCULIN IN THE DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

BY E. C. HORT

THE administration to man of artificially prepared tuberculin has run a strangely chequered course. Welcomed with untempered enthusiasm when announced by Koch in 1890 as a cure for tuberculosis, tuberculin was not long in falling into a disrepute that was due even more to imperfect knowledge of its powers than to the scathing attacks of Virchow and his many followers. To-day, thanks to a host of investigators, we see it fast gaining the position which Koch later claimed for it as a valuable guide to diagnosis and treatment. Of that there can be no question. Any lingering doubt as to the usefulness of tuberculin must disappear on careful study of the innumerable records which the years have accumulated.

Tuberculin then has justified itself, and Koch. This is not, however, to admit that it has no drawbacks or dangers, or that it may safely be recommended for indiscriminate employment. On the contrary, its use is beset with difficulties, a complete and final solution of which we are very far from having attained. Nor can it be said that these difficulties have always received the attention which their collective importance demands. Advocates of tuberculin have not always been careful not to overstate their case. Even the best text-book on the subject, that of Bandelier and Roepke, is not guiltless in this respect. The extraordinary diversity of opinion that prevails as to many practical points in its administration is eloquent of the complexity of the problem. Thus, to quote a few examples only, we are told by competent observers that efficient and safe dosage should not exceed a small fraction of a milligramme of tuberculin T. R. Equally competent workers report that for years they have given with safety and good effect the much stronger preparation T. O. A., in doses half a million times as great. Each worker believes the preparation he has adopted to be the best, yet there are at least six various kinds of tuberculin in common use. *A* declares that even in minimal doses tuberculin should only be administered under the strictest clinical control; *B* affirms that relatively enormous doses require no control beyond that afforded by casual dispensary inspection. The clinical expert relies on his clinical experience to tell him if his administration is correct; the expert of the laboratory declares that as a guide the reaction of the living body is nothing, the reaction of the test-tube all. Calmette teaches us to lean for diagnosis on instillation into the conjunctiva, von Pirquet tells us to trust to scarification of the skin, Koch to

subcutaneous injection. One authority advises that tuberculin administration be reserved for special cases, another that not to use it on a large scale amounts to criminal neglect.

Clearly some definite pronouncement on these and other points, where definiteness is possible, is needed, together with a distinct statement of all such drawbacks to tuberculin, and limitations to its use, as have been revealed by experience. To furnish this practical guidance in broad outline is the chief object of this paper; fuller detail is readily to be found in numerous communications by acknowledged experts. I start with the assumption that while tuberculin is not, and never can be, a panacea for tuberculosis, its value both in diagnosis and treatment has been definitely established. I do not propose to discuss the relative merits of the many forms of tuberculin now to be obtained, because as we do not know the real nature of any form of tuberculin, nor its precise mode of action, the choice of preparation cannot as yet pretend to be anything more than empirical. In general terms, it may be said that for diagnostic purposes preference is usually given to the old tuberculin (T. O. A.), and for therapeutic purposes to the same preparation, as well as to the new tuberculin (T. R.) or the emulsion (B. E.).

### 1. *How to use Tuberculin in Diagnosis.*

The object of the administration of tuberculin is, of course, the production of a recognizable reaction. Four kinds of reaction are possible, and all of them are of service in varying measure as accessories to diagnosis. They are:— (1) The local reaction, the reaction at the site of inoculation. (2) The focal reaction, the reaction at the focus or foci of disease. (3) The general reaction, fever, headache, acceleration of pulse-rate, and other signs of mild intoxication. (4) The reaction *in vitro* of certain of the body fluids, serum, blood, urine, milk, &c., to artificially prepared reagents of the laboratory.

In order to use tuberculin to the best advantage in diagnosis we must know not only how to interpret these reactions, but on what interpretation is based.

With regard to the local and focal reactions we have only recently begun to study immunity reactions in tissues other than the blood. We are now beginning to realize that the local and focal reactions are the expression of an increased susceptibility of the tissues of a tuberculous subject to the action of a substance to which before infection there was little or no susceptibility. The local and focal reactions of tuberculosis are in fact an excellent example of that lowered resistance to the disease on which increased resistance ultimately depends. Anaphylaxis, indeed, is one of the economy's greatest weapons in prophylaxis and in cure, and is of a highly specific nature. It is the detection of the anaphylactic state that is the basis of the diagnostic use of the local and focal reactions caused by tuberculin administration. It is the utilization of the anaphylactic state that makes therapeutic tuberculin administration a rational endeavour. Beyond this we are not at present entitled to go. We do not know

why tuberculin should cause a local, much less a focal, reaction. The theories of Koch, Wassermann, Bruck, Wolf-Eisner, Krehl, and others, on this point, are mutually destructive. Many of the theories offered have left facts far behind.

With regard to the general reaction we know but little more. It is, however, apparently due—and I think recent work<sup>1</sup> of my own published last year tends to support the view—to the absorption of toxic products of the host's own cells which owe their liberation to the action of the inoculated tuberculin on the focus or foci of disease. The process by which this liberation is effected is at present unexplained. This much, however, we understand—that a focal reaction is essentially a hyperaemia of a focus of disease, and that without this focal hyperaemia no general reaction can occur. Now, if the general reaction is due to the absorption of products of the host's own cells, and if the necessary preliminary to that event is focal hyperaemia, itself capable of being caused by inoculation of tuberculin, it follows that an adequate dose of tuberculin in subjects of active tuberculosis causes a true auto-inoculation. In other words, *the real goal of hetero-inoculation is successful auto-inoculation*. Of the explanation of the hyperaemia itself we are ignorant. Consideration of reaction in the test-tube I must for the moment defer.

For purposes of diagnosis tuberculin may be injected under the skin, into the skin, or instilled into the conjunctiva. Injection under the skin aims at a focal reaction, and usually at a general reaction as well. Injection into the skin, or instillation into the conjunctiva, aims at local reaction only. Hypodermic injection is the best method for adults, endermic the best for young children. A focal or general reaction is more trustworthy in adults than in children and less liable to produce untoward results. In quite young children, if an active focus of disease should be present it is clearly better that only a local reaction should be evoked. Hence the value for such of von Pirquet's method. Inoculation into the conjunctiva should only be practised under very exceptional circumstances, if ever, for reasons to be mentioned later. If a general reaction be desired at least three hypodermic injections must be given, with negative results, before any given case can be said to be free from active disease. A good dose to begin with is 1/1,000 c.c. of old tuberculin suspension, proceeding at intervals of two days progressively to a final dose of 1/500 c.c. With proper precautions a rise in temperature of 1° F. in a non-pyrexial subject gives a positive reading. If a focal reaction only be desired a smaller dose must be given, the result of injection being looked for in increase of physical signs, if the focus of disease be accessible to observation. Usually tuberculin is injected in sufficient dose to elicit both a focal and a general reaction. If a safe local reaction be sought, von Pirquet recommends scarification of a small area of the flexor surface of the upper arm, and applies one or more drops of a solution of old tuberculin one part, a 5 per cent. solution of carbolic in glycerine one part, and normal saline solution two parts (Hewlett). The reaction appears within forty-eight hours.

<sup>1</sup> 'Autotoxaemia and Infection,' *Proc. Roy. Soc., Lond.*, 1910, B. lxxxii.

## 2. *How not to use Tuberculin in Diagnosis.*

For purposes of diagnosis tuberculin should not in man be inoculated under the skin unless the following conditions are fulfilled:—(1) All other means of arriving at a diagnosis must have been exhausted because:—(a) the procedure, though reputed to be harmless under skilled clinical and haematological supervision, is not always so, even in the absence of diseases held to be an absolute bar to its use, such as severe nephritis, diabetes, or cardiac disease; (b) in cases of quiescent tuberculosis a positive reaction sometimes results, giving misleading information; (c) a negative reaction does not exclude active disease until at least three injections have been given; (d) in advanced and very advanced cases it often happens that no free so-called anti-body necessary to the production of reaction is present. (2) There must be absence of marked remittent or intermittent fever, because any rise or fall of temperature following the injection is not necessarily the result of the injection. (3) There must be absence also of syphilis, leprosy, and antinomycosis, because in cases of these diseases a reaction may occur even when they are not complicated by tuberculosis. (4) Only the minimal dose necessary to produce a recognizable reaction should be employed. (5) Skilled clinical observation must be available for the detection of any slight increase in the physical signs in a focus of disease, such increase being one of the most valuable signs that a true reaction has taken place. The detection of slight increase of temperature and of pulse-rate, of frontal headache and other signs of intoxication, is less essential because it is often possible by using smaller doses to cause an alteration in the physical signs without eliciting these more easily observed phenomena. In other words, it is sometimes good policy to elicit a focal without producing a general reaction when hypodermic administration is employed.

If tuberculin be injected into the skin it must always be remembered that a positive reaction may occur in quiescent disease. In young children this objection does not necessarily hold, but the older the child the greater the chance of a tuberculous focus, by no means necessarily active, and the smaller therefore the value of the test.

The reasons why tuberculin should not be inoculated into the conjunctiva if it can possibly be avoided are:—(1) that the results in damage to the eye may be disastrous, unless dilute solutions be employed, while the correct dilution for the individual case is difficult of determination; (2) it sometimes happens that subsequent therapeutic injection of tuberculin has to be abandoned because each injection gives rise to a violent conjunctival reaction. The sole merit of Calmette's test lies in the claim that a reaction only rarely occurs in cases of quiescent disease, a claim which appears to be generally upheld.

In connexion with the diagnostic use of tuberculin, whether by inoculation under or into the skin, or into the conjunctiva, it should be borne in mind that in apparently healthy subjects a definite local hypersusceptibility may be

evinced if more than one inoculation be used. When this does occur it may of course vitiate the interpretation of any results obtained.

I now proceed to consider the use and abuse of tuberculin in therapeutics.

### 1. *How to use Tuberculin in Treatment.*

The avowed and immediate object of the therapeutic administration of tuberculin is to produce minimal degrees of focal reaction. The real and ultimate object is to produce adequate but not excessive auto-inoculation. Focal hyperaemia is, as I have already insisted, potential auto-inoculation. It is often, however, laid down that the whole object of tuberculin administration is merely the production of anti-bodies to the injected products of the tubercle bacillus, and that the manufacture of such anti-bodies is the direct result of the tuberculin injection. This theory, for it is no more, misses, I think, the very essence of the true object of tuberculin administration. If it be true that we inject this substance in order to produce safe degrees of focal reaction it is clear that in so doing we are causing the focus of disease to inoculate the system with, *inter alia*, its own products of the tubercle bacillus, and thus are inviting the production of anti-bodies to these focal products. This is a very different matter to placing our hope only on the power of the subcutaneous tissues to produce anti-bodies at the site of injection in direct response to the tuberculin injected. Such a theory also ignores the fact that the focal hyperaemia which makes auto-inoculation possible also allows the opportunity for free and direct access of the anti-bodies thus indirectly produced to the focus of disease. But, more important still, it also ignores the great probability that when an infection undergoes spontaneous cure 'both bacteria and the infected tissues are probably converted into vaccines, which then elicit both bacterial and cellular restraint.'<sup>2</sup> The production of auto-inoculation by tuberculin administration in cases of tuberculous disease is, therefore, the strongest argument for its use that can be adduced from either the clinical or the pathological standpoint. The production of auto-inoculation, natural or artificial, however initiated, is probably one of the chief methods of active immunization in the cure of established tuberculous disease; because the economy, under the stimulus of auto-inoculation, renders absolutely or relatively inert not only the poisonous products of the tubercle bacillus, but also those of the infected tissues of the host. Tuberculin then, after all, is only one method of producing this result, though if other vaccines had the scope of tuberculin, the outlook in some other infections would be bright indeed.

In practice, then, the essence of successful inoculation is the production of mild degrees of hyperaemia which should as a rule be far below the plane of clinical observation. Success in favourable circumstances is to be read in the results of unseen reactions, namely, in clinical improvement. It is here that the difficulty arises of being sure that improvement after injection is due to the

<sup>2</sup> *Rational Immunization*, Bale, Sons and Danielsson, 1909, 73.



injection. The greater the experience of the observer the less will be his inclination to dogmatize on this point. One cannot help feeling that some at least of the benefit which follows the use of extremely small doses of tuberculin is sometimes attributable not to the tuberculin, but to spontaneous reactions occurring independently of administration. It is better, however, to give small doses and wrongly interpret the sequence of events, than without adequate experience give large doses and run a certain risk of doing harm. To ensure safety, in chronic mild pulmonary tuberculosis an initial dose of 1/20,000 of a milligramme of T. R. may be given in adults, gradually increasing to 1/1,000. In more active disease safe limits may be taken as from 1/100,000 to 1/1,000. Occasionally unexpected good results from the production of a well-marked focal and general reaction after larger doses. In tuberculosis of glands, joints, bones, and viscera other than the lungs, slightly larger doses than those mentioned can be given. To ensure the maximum amount of benefit some observers work up to very much larger doses, amounting to 500 or even 1,000 milligrammes of T. O. A. For years this has been the practice on the Continent, and excellent results are reported. In this country, however, the tendency has been to believe that to aim at the maximum amount of benefit carries with it a proportionate increase in risk. Should the dose be excessive, quiescent disease may become active, active disease more active. Until we understand the real nature of tuberculin all rules as to dosage are bound to be unsatisfactory. Meanwhile it is better to lean to the side of caution and leave employment of large doses to the greatly daring. Nor can any precise rules be laid down as to the proper spacing of the injections. Each case must be judged absolutely on its own merits. Whenever there is fever careful study of the temperature chart several days before and after an injection will furnish the most valuable guidance. Before giving the first dose the chart in all such cases should, if possible, be studied for the readings of weeks. The easiest way of doing this, as I showed some time ago, is to plot out a continuous curve of the highest reading in each day. If this be done it is possible to see at a glance that many cases can only be made worse by tuberculin, and that others are doing very well without it. In cases that appear to require it the correct stage at which to inject is often shown. In apyrexial cases control by blood examination will be most useful when a reliable method is available. To this point I shall presently return.

## 2. *How not to use Tuberculin in Treatment.*

For therapeutic purposes tuberculin should not be injected under the skin in the following circumstances:—(1) When the diagnosis is still uncertain. To this rule there are but few exceptions. (2) In the very young or the very old, for obvious reasons. (3) In advanced disease, because the load of uninsulated tuberculin, and of uninhibited cell toxins, is already dangerously high. If in such cases the economy has refused a reaction after a single diagnostic dose it is

not likely that any good can result from stimulus being more frequent than any evidence of response. (4) In any form of tuberculosis where complicating organisms continue to play a prominent part, in spite of measures directly aimed at their suppression, mainly because if the tuberculin treatment in such cases does harm to the tuberculous element the resistance of the latter to the action of the complicating organisms is necessarily impaired. (5) In cases, whether complicated or not by other bacterial infections, where any considerable degree of fever exists, because as a rule such cases bear tuberculin very badly. (6) In generalized tuberculosis, or in the meningeal forms, whether discrete or concrete, for the same reason. (7) In severe cases of diabetes, nephritis, and cardiac disease. (8) In cases where both before and after injection competent clinical observation is not available, supplemented, if possible, but never replaced, by some really satisfactory method of blood examination.

Epitomizing the rules thus laid down for and against the use of tuberculin in diagnosis and treatment it may be said :—(1) That in diagnosis von Pirquet's method is the best for young children, and Koch's subcutaneous method the best for every one else. (2) That a positive reaction after hypodermic injection does not necessarily prove, nor a negative reaction necessarily disprove, the existence of active disease. (3) That neither in diagnosis nor in treatment should tuberculin be injected into the very young, the very old, or the very ill, or in cases of marked fever, or of severe mixed infection. (4) That quiescent disease may be stirred into activity, and active disease into greater activity, if the therapeutic dosage be incorrect. There are two points already touched upon that require further notice, namely, haematological control, and clinical control.

### 1. *Haematological Control.*

In forming a sound judgement as to the wisdom of employing tuberculin in any given case we are greatly hampered by the want of a good method of blood examination. If we are thoroughly to control the need for, and the results of, tuberculin administration, we must have further help of this kind than we can at present command. For controlling tuberculin administration the opsonic method is not an adequate gauge of immunity standards, though for purely diagnostic purposes it has a definite though limited scope. What is urgently needed is some simple quantitative method which, in conjunction with skilled clinical observation, will supply a gauge for diagnosis, prognosis, and treatment. Already steps in this direction have been taken on the Continent, and in this country by d'Este Emery, who has devised and now employs a quantitative serum method,<sup>3</sup> using the haemolytic system as indicator. Now the haemolytic system is no more than the galvanometer, so to speak, recording differences in potential, and is in no way essential to the reaction between antigen and antibody. A simpler method still of measuring this reaction is wanted, one that will give results beyond dispute. Such method I hope shortly to have ready.

<sup>3</sup> D'Este Emery, *Hunterian Lecture on Immunity*, 1911.

If properly used as an adjunct to clinical observation it will, I believe, assist in removing tuberculin administration from the domain of empiricism, and in placing it on a sure scientific basis.

## 2. *Clinical Control.*

This form of control is vital to tuberculin administration for two reasons:— (1) To guard against the production of harmful results; (2) to ensure that no single detail in general treatment suitable to the individual patient be omitted. I need not labour these points. Enough to say that it is impossible to judge of the eligibility of a case for diagnosis by tuberculin unless it has been first determined that none of the unfavourable conditions enumerated above are present. This, as a rule, involves clinical observation for some days prior to inoculation. The same remark applies with even greater force to the therapeutic administration of tuberculin. Here careful watching is necessary not only before treatment is begun, but after each injection as well. Moreover, however excellent may be the results yielded by the administration of tuberculin, it can never be more than an accessory to general methods of treatment. Abundant and suitable food, good air supply by night and day, the judicious regulation of exercise and rest, must always remain of supreme importance. It is only by attention to such factors as these that the average patient's power of response can be effectively utilized. Hence the necessity, in tuberculin treatment, for adequate supervision, without which, indeed, specific treatment were better abandoned. Such supervision can only be adequate when it is thorough, and to be thorough it must be exercised in connexion with the educational control afforded by the hospital, the sanatorium, the consulting room, and, where necessary, visitation in the home.

Tuberculosis, if I may glance once more at the broader and more abstract and more fascinating aspects of this subject, is anatomically a local disease with constant tendency to symptoms of more general disorder. From analogy of the supreme importance of well-regulated hyperaemia in conducing to cure of other forms of local damage, it is unthinkable that a tuberculous lesion should be exempt from a rule to which there is no ascertained exception. To suppose, however, that the effect of focal reaction is merely to stimulate the tubercle bacillus to excite the production of anti-bodies to itself is an altogether inadequate conception of a process that includes other factors of yet deeper significance. Never shall we rightly interpret the functions of substances which, like tuberculin, aim at the re-establishment of immunity until we realize that the ultimate object of inoculation from without is to bring into play that stimulus from within which is the true secret of natural cure, and without which adequate response to all the factors in a centre of disease is impossible of attainment. If we fail to realize this we fail to realize also the central object of the anaphylactic state.

## ON OXYCEPHALY

By H. MORLEY FLETCHER

With Plates 30-38

THE cranial deformity now generally known as oxycephaly is also described under various appellations, such as acrocephaly, 'Thurmschädel,' 'Spitzkopf,' tower or steeple-head, 'turritum caput,' 'tête à la Thersite' (Hamy). The condition does not appear to have attracted attention, except as a curious malformation, until the visual defects so frequently associated with it led to investigations on the part of ophthalmologists. Thus we find that all the earlier accounts of this condition, and there are many of them, appear in the various ophthalmological journals of Europe and this country.

The almost invariable impairment of vision with its frequent accompaniment, optic atrophy, was first definitely recognized and described by v. Graefe in 1866, Michel in 1873, and v. Hirschberg in 1883, and since then a large number of cases of this type, as well as of other cranial deformities associated with optic atrophy, have been recorded, notably by v. Hirschberg, Enslin, and Patry. The bibliography shows that many cases have been recorded; the number cannot be accurately given as some are doubtful and others are re-quoted, but it is probably between eighty or ninety. The condition is not very rare and it is very striking, yet it is surprising that in this country it appears to have met with little recognition by clinicians until quite recently.

My own attention was directed to the condition by a case I met with about eight years ago, at the East London Hospital for Children, in conjunction with my colleague the late Mr. Hancock, and since that time I have been endeavouring to investigate the subject further, as it presents points of very considerable interest.

### *Clinical Aspects.*

The cardinal signs are the characteristically shaped skull, exophthalmos and impairment of vision, sometimes amounting to total blindness, associated with changes in the fundi oculorum.

The aspect of the patient is very striking, the great height of the forehead sloping gradually upwards to the vertex with feebly marked superciliary ridges. The vertex of the skull appears pointed instead of flattened or rounded, and a ridge, or bony prominence, is sometimes felt in the region of the bregma. The hairy scalp may be raised above the normal level and present the appearance of

being perched on the top of a cone. Viewed laterally, the ears appear placed on a lower level than normal. The temporal ridges and depressions are feebly marked.

*The eyes.* Exophthalmos is present in all the well-marked cases. It is sometimes extreme, as in Cases I and VI, and dislocation of the eyeballs in front of the eyelids occasionally occurs. Failure of closure of the eyes, especially during sleep, may lead to lachrymation and conjunctivitis as in Graves's disease. Not infrequently the protrusion of the eyeballs is unequal on the two sides. Divergent *squint* is common and gives a peculiar appearance to the bulging eyes: occasionally the squint is convergent. *Nystagmus* is present in the majority of cases.

*Other facial characteristics.* The nose may be well formed, but in several cases there was a definite deflexion to one side. That shown in Plate 30, Fig. 1 (Case I), is probably largely the result of an accident in quite early life. These photographs show well a marked flattening or depression in the malar and supra-maxillary region, which is very characteristic, though not so commonly present in the juvenile as in adult patients.

The complexion tends to be muddy, sallow, and dark, especially in the older patients. The hair was dark in all the cases I have seen.

They are usually mouth-breathers; the open, gaping mouth adds to the grotesque appearance and gives it a stupid vacant expression. In many cases the palate is shortened and extremely highly arched, as in Cases I and III. The teeth are liable to early caries, the incisors are prominent. The last upper molars may remain unerupted, as in Case I, owing to the shortening of the superior maxilla.

*Intelligence.* This is unimpaired in quite a large proportion of cases, and may be above the average. It is probable that in cases with a mental development below the average this may be due to the ocular defect which develops in early life and produces a backwardness from 'deprivation', to use Ireland's term. One of my cases (Case III) showed a remarkable degree of intelligence: finding that he was unable to distinguish letters he speedily taught himself to read the blind alphabet. Case I never went to school on account of his visual defect; but taught himself to read and write at home with his father's help. Potts states that in examining thousands of mentally defective patients he met with only two cases of oxycephaly.

### *Special Senses.*

*Vision.* This is occasionally unimpaired, but in the vast majority of cases sight is very defective. This depends to a considerable extent on the age of the patient: the younger the case the better the vision. In the adult cases the ability to read type is rare; perception of large objects is the usual condition. Complete blindness may result, but it is difficult to give accurate figures as to the proportion of cases in which this occurs.

*Intra-ocular changes.* The most constant abnormality found is *optic atrophy*. The disks appear greyish, bluish, or ivory white with somewhat irregular edges. The arteries are thin, the veins dilated and tortuous. Optic atrophy was present in six of the seven cases to be described later. In one of Dr. Hutchison's cases included in this series the disks were reported as pale, in one atrophied, and in the third the atrophy was of secondary type. In some cases 'choked disk' has been met with in the early stages of the condition of oxycephaly. In forty-two cases collected by Enslin the atrophy was post-neuritic in thirty-six; in only two of these was it regarded as primary. Friedenwald describes post-neuritic atrophy in nine out of twelve cases. Too much reliance must not be placed on these figures as an indication of the frequency of optic atrophy in oxycephaly, seeing that most of the recorded cases have sought advice on account of failing eyesight. They suffice to show that it is a very frequent occurrence, although not an invariable one. Occasionally pigmentary changes in the retina in the neighbourhood of the disk are met with. Errors of refraction, particularly myopia, are common.

*Smell* is often completely lost. (Meltzer found this in twelve out of twenty cases quoted by Merle.) It was impaired or lost in four out of the seven cases. *Hearing* usually unaffected. *Taste* very rarely affected. The data with regard to these points are not satisfactory, as in many cases they have not been recorded.

#### *Other Malformations or Abnormalities.*

The following have been described in a few cases: Malformations of ears; elbow and shoulder joints, fingers; webbing of toes. Tucker recorded in 1904 a case of oxycephaly in an Indian, in which he noticed a peculiarity of the elbow-joints, which could not be fully extended. I have found this abnormality present in one (Case I) of my cases, and in one of Dr. Hutchison's (Case V). The elbow-joint resists full extension (Plate 31, Figs. 5 and 6). When extended as far as possible, the forearm is deflected outwards. The inner condyle appears to be unduly prominent. This peculiarity requires much fuller observation before any opinion can be given as to its frequency or significance. More will be said about it when discussing the pathology of the disease. In one of these cases (Case I) there is limitation of movement in an upward direction in both shoulder-joints.

Dr. Hutchison and I have met with a very curious malformation of the fingers in two cases (Cases I and V). The first phalanx of each thumb is somewhat thickened, flattened, and sharply curved outwards, with its concavity to the radial side. The little finger in both these cases is curved inwards.

#### *Course.*

An analysis of the recorded cases leads me to the conclusion that they may be divided into three groups. In the *first*, exophthalmos and the deformity of the head are definitely present at birth, and in some of these cases total

blindness. These may be classed as congenital cases; they are comparatively few in number, and form but a small proportion of the total. In a *second* group may be placed the cases in which during the first few months of life changes in the shape of the head develop, and the eyes are noticed by the parents to be 'large'. In the course of the first two years these signs become more marked and are attended by gradually increasing impairment of vision. The exophthalmos and the lofty shape of the head become increasingly evident as growth proceeds. The *third* group includes those cases which appear to be quite normal for the first few years of life and the earliest signs may not appear before the second to the sixth year. In these cases an increasing visual defect is usually the first symptom. Vision may remain unimpaired till the fifth to sixth year.

It is interesting to note that in some cases the onset of the condition appeared to date from a fall, or a blow on the head. Patry records two such cases in which this occurred at the age of four years. (Compare Dr. Hutchison's case, VII.)

A consideration of the recorded cases leads me to agree with Patry that the ocular defect begins in the first five years. The impairment of vision is progressive and sometimes ends in total blindness, but in most cases perception of light or of large objects remains. Fair vision may remain with extreme exophthalmos and very definite optic atrophy as in Case I.

As growth proceeds, the lofty shape of the head becomes increasingly evident and exophthalmos develops. Headache is a very common symptom, and may be very severe. In one of my cases it was frontal and vertical. It is often occipital. Vertigo is less frequently met with. Fits have been recorded in a few cases in young children, but it is difficult to be certain as to how far these fits are connected with the cranial condition.

*Duration.* As far as the evidence serves there is nothing to show that oxycephaly shortens life, but it is a noteworthy fact that few, if any, typical cases have been recorded in patients over fifty years of age.

#### *Predisposing Causes.*

*Race* does not appear to have any influence. In this series of seven cases, four were Hebrews; this high proportion is probably explained by the fact that the cases were drawn from hospitals in the East End of London attended by large numbers of this race. The recorded cases include most of the European races.

*Syphilis* and *Rickets* cannot, in the writer's opinion, be regarded as important factors, though some writers (Meltzer and Potts) consider that rickets plays an essential part in the pathology of oxycephaly.

*Sex.* This may be said to be the only important predisposing factor, as the condition is much more common in males than females. Patry gives a series of sixty-four cases in which only seven were females (this series includes some cases which were not true cases of oxycephaly).

*Heredity* is very rarely a factor. v. Hirschberg records a case whose maternal

grandfather was similarly affected. Weiss and Brugger mention two oxycephalic brothers seen by Oeller. Hanotte states that Hamy met two oxycephalic sisters. The mother of one of my cases (Case I) had a malformed head, exophthalmos, and defective vision.

### *Morbid Anatomy.*

Almost the whole of our knowledge of the morbid anatomy of oxycephaly is derived from the study of dried skulls in museums, the histories of which are almost without exception unobtainable. Very full investigation of the special features of the oxycephalic skull has been made, notably by Hanotte, Patry, Enslin, and others, and the peculiarities found in this condition are constant and characteristic. Through the kindness of Professor Keith I have been able to examine the specimens in the museum of the Royal College of Surgeons, which contains several good examples. Very few, probably not more than three, cases of oxycephaly have been recorded with a post-mortem examination.

In this country Power (1894) recorded a case described as oxycephaly in an infant which lived four weeks, the head of which is preserved in the museum at St. Bartholomew's Hospital, and in 1901 Carpenter described another case, also in an infant, the head of which is in the museum of the Royal College of Surgeons. It is very doubtful, in the writer's opinion, whether either of these cases, particularly that of Carpenter, should be classed as oxycephaly, but rather as foetal monstrosities, as there was no evidence of premature synostosis.

The dried skulls which have been examined belonged mostly to adults, and present the following features:—There is a great increase in the vertical height due to the alterations of shape of the vault. The superciliary ridges and frontal prominences are absent or much reduced and the frontal region rises steeply upwards to the bregma. The frontal and mastoid sinuses are often absent. The temporal fossae are shallow. The characteristic abnormality found is the evidence of premature synostosis of certain sutures. Of these the coronal and sagittal sutures are chiefly involved. The coronal suture is generally completely closed, but sometimes is found to be ununited for a short distance, 2–5 cm., on each side of the bregma. The sagittal suture is usually synostosed. The bregma is often marked by a distinct prominence or bulging. The metopic suture is synostosed. Other sutures are frequently involved, but to a much more varying degree than those already mentioned, but generally speaking those of the vault are the ones most affected. The orbits present striking features. The depth is much reduced, the external part formed by the greater wing of the sphenoid appears to have been pushed forwards. The orbital axes are very oblique downwards and outwards.

*The brain.* Papillant investigated the condition of the brain in a case of oxycephaly. Bourneville's case was not a case of pure oxycephaly. In Papillant's case the convolutions, more particularly of the lower portion of the brain, showed obvious signs of pressure, while the reverse was manifest in the



upper part of the frontal and parietal lobes. The convolutions with an antero-posterior direction appeared to show arrested growth and were very difficult to separate. The horizontal branch of the Sylvian fissure was very short.

The superior maxilla is very poorly developed, as well as the lateral walls of the nasal chamber, especially in the vertical direction. The nasal septum is generally deviated, probably in part as the result of these changes and also owing to a pushing down of the base of the skull (basisphenoid and mesethmoid). The total length of the superior maxilla is reduced in proportion to the anterior posterior diameter of the skull.

Some writers have described a narrowing of the optic foramen, but the evidence appears to be against this. The hard palate is sharply arched. The antra may be rudimentary. At the base the condyles are sometimes less prominent than normal. The basilar process is much shortened. The cranial fossae show great changes in size and shape; they are deepened and widened. The middle fossae exhibit this to a striking degree, and this is well shown in the appended skiagrams. The sella turcica is widened and deepened in its central portion. The inferior maxilla does not present changes that can be regarded as characteristic. On holding an oxycephalic skull to a bright light the bones of the vault and of the fossae appear more transparent than those of a normal adult skull, and the so-called 'digital markings' to be referred to later can sometimes be faintly distinguished by transillumination in this way. Measurements of oxycephalic skulls have been very fully made in long series of cases by several writers, particularly Patry, and reference should be made to his work for information on this point.

*X-ray appearances.* Another method of examining the changes in the skull is by means of the X-rays. Grunmach (v. Hirschberg and Grunmach), Bertolotti, Dorfmann, and others have described the appearances met with which generally confirm in the living subject the existence of the changes already described in dried skulls. All those who have investigated cases of oxycephaly by this method have noticed certain abnormal features which may be regarded as constant. The structure of the bones of the skull, especially those forming the vault, instead of presenting a fairly uniform density in the skiagram show certain markings or depressions resembling a coarse network, and giving the shadow of the bone a dimpled appearance.

These areas, or 'digital markings' as they are called, are most obvious in the frontal region, although they may be clearly visible over the whole vault and in the basal fossae, where they differ from the appearances in cranio-tabes in that they are more diffuse, larger, more numerous, and less sharply defined. These 'digital markings' are occasionally seen in apparently normal skulls, but never, so far as the writer can ascertain, in the same degree as in oxycephaly. They have been generally attributed to pressure exerted by the brain on the skull, and the markings are regarded as corresponding to the convolutions. This explanation does not appear to the writer to be entirely satisfactory, as, in the first place, in another condition, hydrocephaly, the pressure

exerted on the cranial bones does not usually give rise to a similar appearance. For purposes of comparison a skiagram was taken from a patient, aged 52, suffering from effects of old hydrocephaly, and examined. In this the bone presented a much more uniform structure, and in spite of the reduction of thickness the digital markings were absent; the examination made of skiagrams of juvenile hydrocephaly showed exactly the same appearances. Secondly, it is difficult to accept without further evidence the hypothesis that these areas or large dimples correspond to the convolutions, as the markings would appear to be too numerous and too small. The writer prefers to regard them as an indication of some change in the actual structure of the bone due to abnormal growth, the nature of which is at present quite obscure. Leonard, discussing the Röntgen diagnosis of hydrocephaly, describes a case of hydrocephaly in which the inner table of the skull showed depressed areas, visible by ordinary light, exactly corresponding to the convolutions. He says it is only in the late form of hydrocephaly occurring after the sutures have become ossified that the pathological change takes place in the inner table. Such a condition cannot be common in oxycephaly, seeing that in the large number of skulls examined by different writers irregularity or unevenness of the inner aspect of the vault is hardly mentioned.

The skiagrams show that the frontal sinuses and antra are either absent or so rudimentary that they can barely be distinguished. The bones forming the orbital, nasal, and superior maxillary regions present an extraordinarily transparent flocculent appearance. The superior maxilla in the skiagram of Case I is greatly shortened and the last molar can be seen lying above, unerupted. The lower jaw is underhung, and is shorter and squarer than normal. The bone of the inferior maxilla appears to be of fairly normal density.

The sella turcica presents the most striking appearance; it stands out with unusual clearness and seems to be considerably enlarged and displaced backwards. The bones forming the vault show some reduction in thickness, especially in the region of the bregma, where there is often a distinct bulging. This is well seen in the skiagrams of Cases I and VI. In both there is obvious localized bulging at the vertex. For the purposes of comparison a skiagram of a normal adult skull is given (Plate 38, Fig. 23).

*Other associated defects.* Reference has been made to an abnormality of the elbow-joints in two of the appended cases. This defect was present in one of my cases (Case I) in which there was a deformity of the elbow-joints with inability of full extension. The same was noticed in one of Dr. Hutchison's cases (Case V). In Case II the head of the ulna appears to be thickened. This condition requires further observation as to its frequency and nature.

I must take this opportunity of thanking Dr. Walsham and Dr. Pirie of St. Bartholomew's Hospital for the excellent skiagrams they have taken of my series, and Mr. Scott of the London Hospital for those of Dr. Hutchison's cases. I am also indebted both to Professor Keith and Dr. Addison for kind suggestions on various points of anatomy.

*Pathology.*

The idea has long been held and is still widely prevalent that oxycephaly is essentially a congenital deformity of the head and that the chief point of interest consists in the ocular affections associated with it. Reasons will be advanced later against this point of view and in favour of the condition being regarded as a manifestation of a definite morbid process affecting more manifestly the bones of the skull than other parts of the body.

A brief review may be given here of the various hypotheses which have been advanced in explanation of the malformation of the skull. Most writers on the subject are agreed that the characteristic deformity of the skull is due to premature synostosis of certain sutures, notably the sagittal and coronal. The evidence in favour of this synostosis is very strong, as it is found in all the skulls which have been examined. The last portions of these sutures to become synostosed are those in the neighbourhood of the bregma. In some cases of oxycephaly in young subjects the anterior fontanelle has been found to be patent. As a result of the premature union of these two sutures the growth of the vault of the skull is restricted in both its antero-posterior and transverse diameters, and to accommodate the increasing bulk of the brain a compensatory increase in height takes place. Eventually the anterior fontanelle closes, but there is reason to think that this occurs at a later date than the normal, and its former site is marked by a slight protuberance with thinning of the bone, as is well shown in several of the skiagrams. The rapidly growing brain is partly accommodated by the compensatory increase in the vertical diameter, but in addition important changes are brought about at the base. The cranial fossae, especially the middle one, become deepened and thinned out by the pressure exerted by the brain. The thinnest bones naturally are most affected, and thus the orbits become deformed and shallow, the greater wings of the sphenoid in particular being pushed forward by the sphenoidal lobes, so that, as Weiss and Brugger describe it, they form the posterior instead of the lateral walls of the orbits. The temporal region is pushed outwards so that the temporal fossae become shallow or obliterated. The malformation of the vault, the cranial fossae, and the orbits may be accounted for in this way: the other bony changes will be discussed later.

*What is the cause of this premature synostosis?* Virchow and v. Hirschberg and others regarded the primary cause as some form of meningitis, but the evidence in favour of it is very slight. Some thickening of the pia arachnoid has been met with in one case. A diffuse meningitis would have been expected to give rise to hydrocephaly or to microcephaly with mental defect. The absence of any mental defect in the great majority of cases is in the writer's opinion a strong argument against the occurrence of meningitis of any known type.

Hydrocephaly has been advanced as a cause of the synostosis. Meltzer suggested that it was due to a reaction process in rachitic bones to the pressure

of hydrocephaly, and that after synostosis has taken place resorption of fluid occurs. Potts, in a recent paper (1910), does not accept the view that premature synostosis is a sufficient explanation of the deformity, and ascribes it to a special form of hydrocephaly, but without giving, in the writer's opinion, any evidence of its existence. A study of the recorded cases leads one to exclude rickets at any rate as an important factor in the disease. It appears to the writer that there are also cogent reasons for excluding hydrocephaly as a cause of oxycephaly. The shape of the head, the unimpaired intelligence, the absence of paralyses, the fact that such sutures or fontanelles that have been observed to be patent in the younger cases are not described as bulging, are strong arguments against this view. Further, the cerebro-spinal fluid has been examined in a few cases of oxycephaly (Behr), and was found to be normal, and the pressure was not increased. To investigate further the possible relation of hydrocephaly to oxycephaly, Dr. Walsham kindly took for me a skiagram of the head of an adult hydrocephalic patient, aged 52, for comparison with that of the adult oxycephalic cases. The bones of the skull presented a totally different appearance; they were uniformly homogeneous and did not show the 'digital markings' met with in oxycephaly, and further, even at this age, the sutures were still ununited. The same may be said of the skull of a hydrocephalic child I have recently examined.

What is the cause of this premature synostosis if it is not due to some form of meningitis, a rachitic condition of the bones, or hydrocephalic pressure? In the writer's opinion it depends upon some deeper underlying cause, the nature of which at present remains obscure, and in his opinion the term 'oxycephaly' is a misleading one, as it implies as the essential condition deformity of the head. It seems probable that the condition should be looked upon from a wider point of view, the changes in the bones of the skull being only one of its manifestations and the most obvious. Bertolotti has recently made a valuable contribution to our knowledge of the subject; in this he regards oxycephaly as '*un syndrome osseux qui peut être bien plus étendu que ne voudrait signifier son nom, et qui correspond, non pas seulement à des altérations de la calotte, mais aussi de la base du crâne, des os de la face et enfin de plusieurs autres parties du squelette*'.

With this the writer is in agreement, although he does not agree with Bertolotti that oxycephaly is a dystrophy of rachitic origin. It is a noteworthy point that nearly all those who have investigated the skiagraphical appearance of the skull have noted the extraordinary changes which are present in the sella tureica, and it may possibly be shown that the alterations in the structure and density of the bone and premature synostosis may be the result of some change or abnormal development in the pituitary body. This must of course be regarded as a mere conjecture, for no post-mortem observations have been made with regard to it.

Professor Keith's recent lectures on 'Prehistoric Man' and the suggestions he has made as to the possible part played by the pituitary body in the

development of racial characteristics may be brought forward in this connexion. The skull is not the only part involved in the condition of oxycephaly; other parts are also affected. There are many points which require investigation, notably the histological features of the affected bones and the alterations and changes in the joints such as were present in Case I.

*Cause of the optic atrophy.* A brief summary must be given here of the various explanations of the optic atrophy which is almost invariably present: Virchow regarded it as secondary to a neuritis due to some form of meningitis; Ponfiek and others, that it is due to papillary stasis caused by narrowing of the optic foramen. Friedenwald considered that the papillitis and atrophy are the result of direct pressure exerted, owing to the synostosis, by the growing brain comparable to that in cerebral tumour. This view is also held by Dorfmann, who points out as a result of examination of skiagrams, that, as the changes at the base of the skull advance, the optic chiasma becomes unduly exposed to pressure.

Behr suggests that intracranial pressure provokes a stasis of the papilla, and that the peripheral fibres of the optic nerve undergo atrophy, leading to concentric diminution of the visual field. Atrophy of these peripheral fibres takes place with resulting diminution in size of the nerve and relief of pressure. In this way he explains the comparative rarity of complete blindness.

The writer inclines to the view that the optic atrophy is the direct result of pressure exerted by the growing brain. The cases of oxycephaly in which papillitis or optic atrophy is absent are explained by the compensatory expansion of the skull in abnormal directions being adequate for the increasing growth of the brain.

### *Treatment.*

So far as is known there is no treatment for the cause of oxycephaly. Headache, which is such a frequent symptom, was relieved in two of my cases by the administration of potassium iodide. Operative treatment has been employed with a view to save the sight. One of Dorfmann's cases, a girl aged 4, had well-marked papillitis and suffered from severe headaches and insomnia. In 1907 Eiselsberg trephined her. The bone was found to be then  $1\frac{1}{2}$  mm. in thickness, the dura mater normal, the veins distended. Three weeks later the swelling of the disks had diminished 1 diopter, and the headache and sleeplessness were relieved. Trephining to relieve pressure would seem a reasonable method of treating cases of oxycephaly in children when papillitis without atrophic changes is present, as probably all such cases subsequently become practically if not completely blind.

Before proceeding to the detailed account of the series of seven cases, I must express my gratitude to Dr. Robert Hutchison for permitting me to include his three cases in this series, and for the trouble he has taken in procuring the photographs and skiagrams which illustrate them.

*Case I.* A. R., male, 23, storekeeper: photographs (Plate 30), skiagram of skull (Plate 31). Did not know at what age the exophthalmos or head deformity began. Eyesight defective as long as he could remember, and always worse in left eye. Never went to school, owing to bad eyesight, but taught himself to read and write with his father's help. Did not suffer from headache and had never had fits. His mother (whom I have seen) had exophthalmos and malformation of the superior maxilla, but the vault of the cranium was not definitely oxycephalic. Parents English.

Head typically oxycephalic (photographs, Plate 30). The bregma was prominent. Extreme proptosis; the right eye was more prominent than the left and occasionally became dislocated forwards in front of the eyelids. Divergent squint and nystagmus, could distinguish only moving objects with left eye, can read print with right eye. Mr. Holmes Spicer reports: 'Right pupil unusually small, but reacts normally. Left pupil larger than right and insensitive to light. Both optic disks very white; the *right* disk has ill-defined edges and a definite white fibrosis-looking prolongation up and inwards suggesting a previous neuritis; the lamina cribrosa also is not visible, but the vessels are quite clear. The *left* disk is quite clear and the vessels well defined—the lamina cribrosa is not seen. The condition of the disks is quite compatible with previous neuritis. Right visual field much reduced.'

The nose was strongly deflected to the right; this was stated to be the result of an injury. The superior maxilla was very deformed, it was shortened from before backwards. The hard palate formed a narrow, very pointed arch. The second and third molars were absent in the upper jaw and could be made out in the skiagram lying above in what appeared to be the rudimentary antra. Lower jaw underhung, teeth normal in number. Sense of smell lost. Hearing and taste normal.

*Elbows* could not be fully extended (Plate 30, Fig. 3, and Plate 31, Figs. 5 and 6). Internal condyles unduly prominent, some creaking in the joints: the head of both radius and ulna appears thickened. He could not raise the arms to the horizontal; obvious creaking in both shoulder-joints, but no change found in the bones. No other malformations present.

Skiagram (Plate 31, Fig. 4) of the skull shows very distinctly the bulging and thinning of the bone in the bregmatic region (?) and the digital markings over the whole of the vault. The most striking abnormality is the altered shape and depth of the middle fossa, and the pushing forward of the posterior wall of the orbit. The sella turcica is pushed backwards and is deepened (cf. skiagram of normal adult skull, Plate 38, Fig. 23).

Dr. R. J. Gladstone very kindly took the following measurements of this case two years ago:—

Height, 5 ft. 2½ in. (1522 mm.).

Circumference of head, 506 mm. Longitudinal arc, 345 mm. Transverse arc, 352 mm.

Diameters of head: L. 179 mm. B. 138 mm. H. 143 mm. Mi. F. 106 mm.

'Index of size' of head, 3532. (The average 'index of size' of males, 5 ft. 3 in. height, is 3850.)

Cephalic breadth index, 76.

Cephalic height index, 79.8.

Horizontal arc, measured from the centre of the external auditory meatus round the sub-nasal point to the centre of the meatus of the opposite side = 231 mm. (Average about 255 mm.)

Average diameters of head in fifty male subjects, aged 20 to 46, measured in the post-mortem room, Middlesex Hospital:—

Length: glabella to occipital point . . . 190.8 mm.

Breadth: greatest transverse diameter . . . 149.5 mm.

Height: bi-auricular line to vertex . . . 134.8 mm.

There is thus considerable diminution in the length and breadth, and increase in height.

	Normal	Case A. R.
Average cephalic breadth index . . . . .	77.6	76.0
" " height " . . . . .	70.0	79.8

*Case II.* E. T., female, 44, charwoman: photographs and skiagram of skull (Plate 32). Did not know when the deformity of the head began. Blind in left eye as long as she could remember. Had suffered with headache, usually vertical, all her life. Single. No past illnesses of importance. One of twins, the other having died in infancy. English descent.

Typically oxycephalic: dark sallow complexion, greasy skin. Nose deflected to left. Hard palate asymmetrical. Distinct exophthalmos; divergent squint; some nystagmus; blind in left eye; pupils react normally. Mr. Holmes Spicer reports on the eyes: 'Some fibrous vitreous opacities; both optic disks very white, having a convex or heaped-up appearance and with a somewhat uneven edge in the left eye. Marked whitening of the veins in both eyes extending far out from the disk. In the central region of both is a large number of small deposits in the choroid, smaller in the right than the left (?hyaline bodies). Visual field of right eye greatly diminished.'

Sense of smell defective. Taste and hearing good. No malformation of the limbs or extremities.

*Case III.* J. P., male, 15: photographs and skiagram (Plate 33). Hebrew. Up to 4 years of age was like other children, according to his mother's account, and the eyes and head were natural. Then the sight began to fail and the head gradually altered its shape and the eyes became prominent. Never fits—suffered from frequent headache. Past and family history good. Very intelligent, learned blind reading at an early age. Typical oxycephaly with exophthalmos, divergent squint, and marked nystagmus. Could barely distinguish large objects. Slight deflexion of nasal septum. Hard palate arched but not nearly so deformed as in Case I. Hearing, taste, and smell normal. There were no other malformations. The skiagram shows the same features as in Case I, the distinct digital markings and the changes in the orbits and the base.

*Case IV.* J. R., male, 14: photographs and skiagram (Plate 34, and Plate 35, Fig. 16). Eyes large at birth and head noticed to be peculiarly shaped. Suffered from frequent occipital headaches. Had never had fits. Memory not good and was only in fourth standard. Was the first and only child, difficult labour, breech presentation. Family history good.

Oxycephalic skull. Exophthalmos and divergent squint. No nystagmus. Mouth-breather. Nasal septum deflected. Superior maxilla shortened. Vision good. No optic atrophy. Ear poorly developed, tragus rudimentary. Sense of smell, taste, and hearing normal.

Peculiar malformation of thumbs; the first phalanx was curved outwards towards the radial side, the outer or radial side being shorter than the inner.

The skiagram of the skull shows very distinctly the characteristic changes at the base and the digital markings.

*Case V* (Dr. Hutchison's case). H. F., female, 5. (Plate 35, Fig. 17.) Parents English. Youngest of seven, others normal; two died in infancy. Three miscarriages, one a monster with 'head like a cow'. Full term child. Was born with prominent eyes and misshapen head. Previous health good. Never fits. Oxycephalic head with flat occiput, prominent bregmatic region. Exophthalmos, divergent squint, defective vision, optic disks atrophic. Mouth-breather; palate highly arched; superior maxilla shortened from before backwards. Elbows could not be fully extended as in Case I; internal condyle prominent. The skiagram

showed thickening of the heads of both radius and ulna. Thumbs shortened; first phalanx curved outwards as in Case IV; only two phalanges in left index finger, one long and a short terminal. Toes webbed and great toes very short.

Intelligence good. Taste and hearing good: sense of smell appears to be defective.

Skiagram of head not obtained.

*Case VI* (Dr. Hutchison's case). S. F., female, 12. (Plate 36.) Ninth of ten children. Rather difficult full term labour. Mother had a severe fright in the sixth week of pregnancy. Jewish parents. Deformity of head and prominent eyes noticed at birth, could see till three years old.

Oxycephalic head. Exophthalmos with divergent squint. Constant, irregular, chiefly lateral movements of the eyes. Pupils react sluggishly to light. One of the eyeballs became dislocated forwards on one occasion. Disks show well-marked atrophy of secondary type with white lines along course of vessels: cannot see light. Sense of smell lost, taste good, hearing somewhat impaired. Suffers from severe headaches. Is said to be 'very clever'. Adenoid facies; high narrow palate; tubercle of Atlas very prominent; thumbs very broad; little fingers kinked like those of a Mongol; viscera normal.

Skiagram of skull (Plate 36, Fig. 20). Bulging in bregmatic region. Digital impressions very well marked.

*Case VII* (Dr. Hutchison's case). M. W., male, 9. (Plate 37.) Said to have been normal at birth. At 18 months had convulsions while teething, which recurred at intervals for 3 months. Had a fall and whooping-cough about this time, when sight was first noticed to fail. Born in Warsaw. The boy is clever, can find his way anywhere, and is distinctly musical. Mother had three miscarriages. Marked oxycephaly: bregmatic region pointed. Circumference of skull, 19 inches; coronal suture, 13 inches. Vision very defective. Optic atrophy. Can distinguish light and dark, but cannot see fingers. Hands, feet, and viscera normal.

Skiagram shows very strongly marked 'digital impressions'. The vault is thin in the bregmatic region.

#### REFERENCES.

1. Algyogyi, H., *Wiener med. Wochenschr.*, 1908, lviii. 1942.
2. Atgier, *Bull. et Mém. Soc. d'anthrop. de Paris*, 1901, 5<sup>e</sup> sér., ii. 95.
3. Beaumont, W. M., *Trans. Ophthal. Soc. U. K.*, 1910, xxx. 44.
4. Behr, *Archives d'Ophthal.*, 1910, xxx. 714.
5. Behr, *Ann. d'Oculistique*, Paris, 1910, cxliv. 217.
6. Bertolotti, *Presse médicale*, Paris, 1910, ci. 946.
7. Bourneville et Boncour, *Bull. et Mém. Soc. d'Anthrop. de Paris*, 1902, 5<sup>e</sup> sér., iii. 35.
8. Carpenter, G., *Proc. Roy. Soc. Med.*, 1908-9, ii, 'Sect. Dis. of Children,' 45.
9. Carpenter, G., *Trans. Ophthal. Soc. U. K.*, 1909, xxix. 157.
10. Carpenter, G., *Reports Soc. Study of Dis. in Children*, Lond., 1901, i. 110.
11. Coats, G., *Trans. Ophthal. Soc. U. K.*, 1907, xxvii. 211.
12. Cohen, C., *Klin. Monatsbl. für Augenheilk.*, 1906, N. F., ii. 517.
13. Dodd and McMullen, *Lancet*, Lond., 1903, ii. 1665.
14. Donaldson, E., *Trans. Ophthal. Soc. U. K.*, 1903, xxiii. 264.
15. Dorfmann, R., *Archiv für Ophthal.*, Leipz., 1908, lxviii. 412.
16. Dorrell, E. A., *Trans. Ophthal. Soc. U. K.*, 1910, xxx. 158.
17. Enslin, *Archiv für Ophthal.*, Leipz., 1904, lviii. 151.
18. Enslin, *Ophthalmoscope*, 1904, ii. 233.
19. Fletcher, H. M., *Proc. Roy. Soc. Med.*, 1908-9, ii, i. Clin. Sect., 113.
20. Ford, R., *Ophthalmoscope*, 1907, v. 199.



21. Friedenwald, H., *Amer. Journ. Med. Sci.*, 1893, N. S. cv. 529.
22. Friedenwald, H., *Archives of Ophthalm.*, N. York, 1901, xxx. 405.
23. Gräfe, A., *Archiv für Ophthalm.*, Berlin, 1866, xii, Abth. ii. 114.
24. Groenouw, A., *Gräfe-Sämisch's Handb. der Augenheilk.*, 2. Aufl., 1904, xi, Abth. i. 257.
25. Hanotte, M., *Thèse de Paris*, Paris, 1898.
26. Harman, N. B., *Trans. Ophthalm. Soc. U. K.*, 1910, xxx. 106.
27. v. Hirschberg, J., *Centralbl. für Augenheilk.*, 1883, 1.
28. v. Hirschberg, J., und Grunmach, E., *Berl. klin. Wochenschr.*, 1909, xli. 191.
29. Hutchison, R., *Proc. Roy. Soc. Med.*, 1909-10, iii, 'Sect. Study Dis. Children,' 125.
30. Krauss, W., *Zeitschr. für Augenheilk.*, 1907, xvii. 432.
31. Krauss, W., *Ophthalmoscope*, 1908, vi. 530.
32. Leonard, *Archives of the Röntgen Ray*, 1911, xv. 336.
33. Manz, *Bericht über die 19. ophthalm. Versamml.*, Heidelberg, 1887, 18.
34. Meltzer, *Neurol. Centralbl.*, Leipz., 1908, xxvii. 562.
35. Merle, P., *Nouv. Iconog. de la Salpêtrière*, Paris, 1908, xxi. 349.
36. Michel, J., *Archiv für Heilkunde*, 1873, xiv. 39.
37. Morax et Patry, *Ann. d'Oculistique*, Paris, 1904, cxxxii. 120.
38. Moutier, *Revue neurologique*, Paris, 1908, xvi. 1258.
39. Nettleship, E., *Trans. Ophthalm. Soc. U. K.*, 1904-5, xxv. 383.
40. Nettleship, E., *Trans. Ophthalm. Soc. U. K.*, 1887, vii. 222.
41. Oberwarth, E., *Archiv für Kinderheilk.*, 1905, xlii. 79.
42. Oliver, C. A., *Amer. Journ. Med. Sci.*, N. S., 1902, cxxiii. 4.
43. Oppenheim, *Lehrbuch der Nervenkrankh.*, 1905, 741.
44. Papillant, *Revue de l'École d'anthropologie de Paris*, 1903.
45. Paton, L., *Trans. Ophthalm. Soc. U. K.*, 1904-5, xxv. 364.
46. Paton, L., *Trans. Ophthalm. Soc. U. K.*, 1907, xxvii. 215.
47. Patry, A., *Thèse de Paris*, 1905.
48. Patry, A., *Recueil d'Ophthalm.*, Paris, 1906, 3<sup>e</sup> sér., xxviii. 158.
49. Patry, A., *Ann. d'Oculistique*, Paris, 1906, cxxxv. 314.
50. Patry, A., *Recueil d'Ophthalm.*, Paris, 1906, 3<sup>e</sup> sér., xxxviii. 156.
51. Ponjick, *Breslauer ärztl. Zeitschr.*, 1885, vii. 54.
52. Potts, W. A., *Reports Soc. for Study of Dis. in Children*, Lond., 1908, viii. 407.
53. Power, H., *Trans. Ophthalm. Soc. U. K.*, 1894, xiv. 212.
54. Rau, *Sitzungsber. d. Berliner ophthalm. Gesellschaft*, Mai 1899.
55. Schuller, G., *Centralbl. für Augenheilk.*, 1881, v. 236.
56. Stephenson, S., *Proc. Roy. Soc. Med.*, Lond., 1908-9, ii, 'Sect. Study Dis. Children,' 229.
57. Stephenson, S., *Brit. Journ. of Children's Diseases*, 1905, ii. 491.
58. Stood, *Klin. Monatsbl. für Augenheilk.*, 1884, xxii. 248.
59. Terrien, *Brit. Journ. of Children's Diseases*, 1910, vii. 176.
60. Tucker, E. F. G., *Lancet*, Lond., 1904, ii. 88.
61. Uhthoff, W., *Klin. Monatsbl. für Augenheilk.*, 1905, xliii. i. 1.
62. Velhagen, K., *Münch. med. Wochenschr.*, 1904, li. 1389.
63. Velhagen, K., *Ophthalmoscope*, 1905, iii. 83.
64. Videcky, *Zeitschrift für Augenheilk.*, 1907, xviii.
65. Vortisch, *Inaug. Diss.*, Tübingen, 1901.
66. Vossius, A., *Klin. Monatsbl. für Augenheilk.*, 1884, xxii. 172.
67. Weiss, L., and Brugger, O., *Archives of Ophthalm.*, N. York, 1895, xxiv. 55.



FIG. 1



FIG. 2





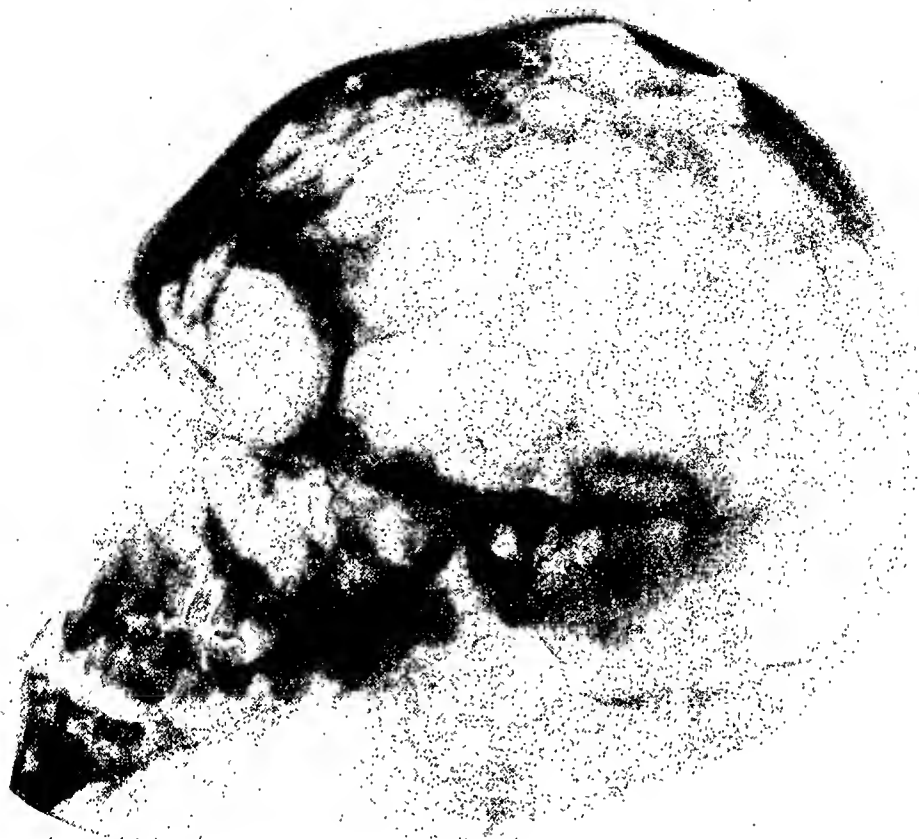


FIG. 4



FIG. 5



FIG. 6





FIG. 7



FIG. 8



FIG. 9





FIG. 10



FIG. 11



FIG. 12







FIG. 13



FIG. 14

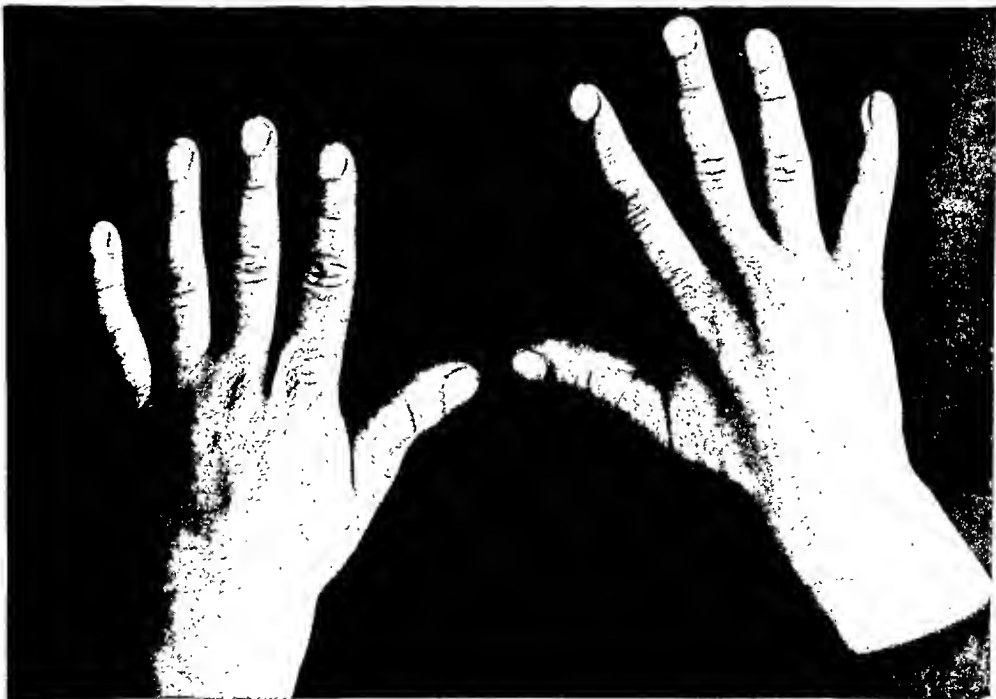


FIG. 15



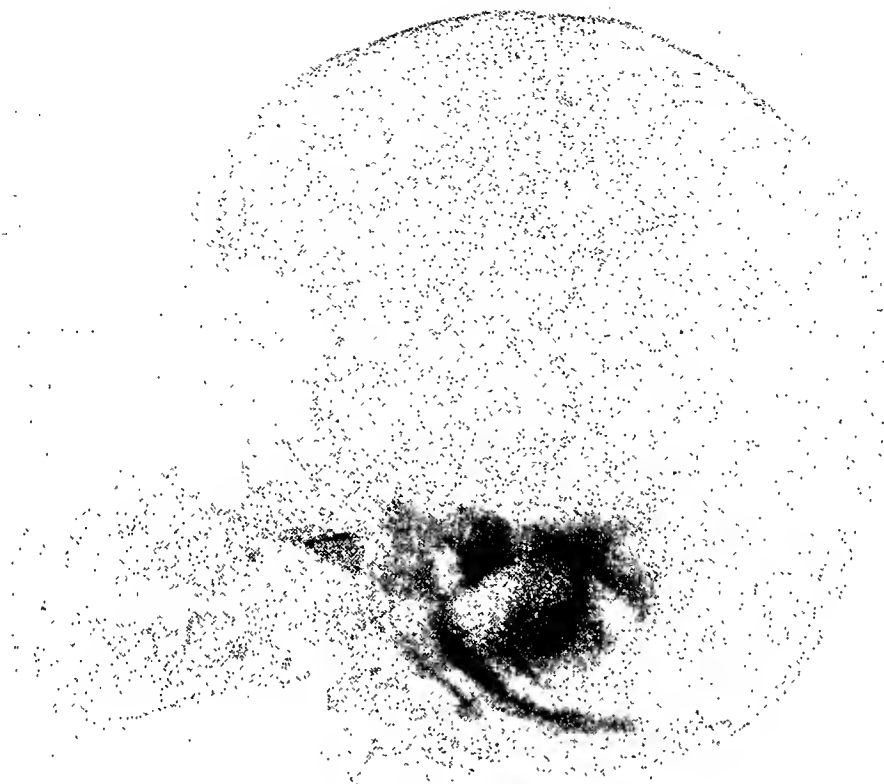


FIG. 16



FIG. 17





FIG. 18



FIG. 19

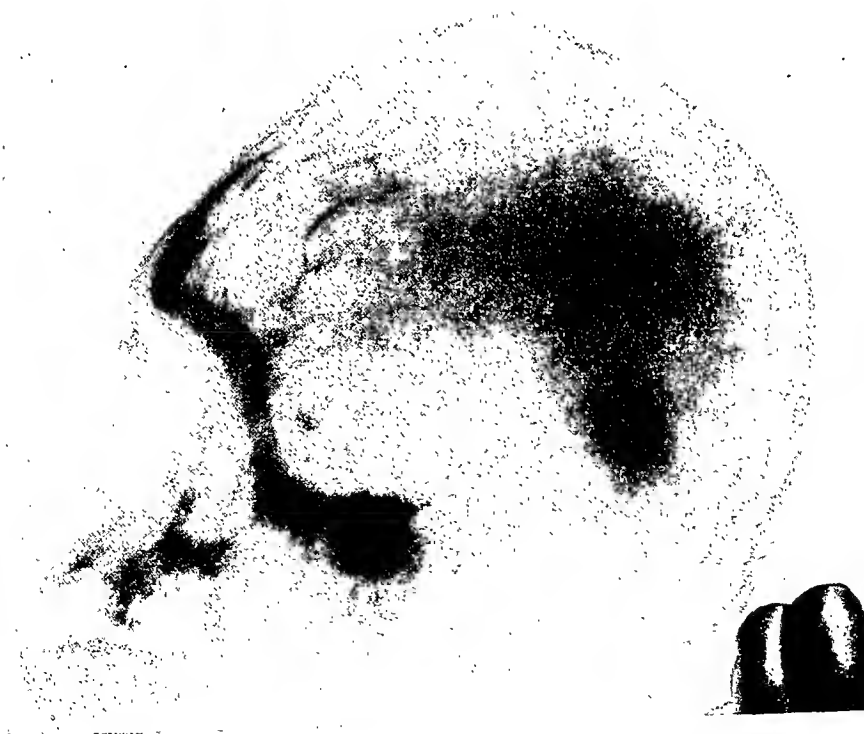


FIG. 20





FIG. 21



FIG. 22







FIG. 23

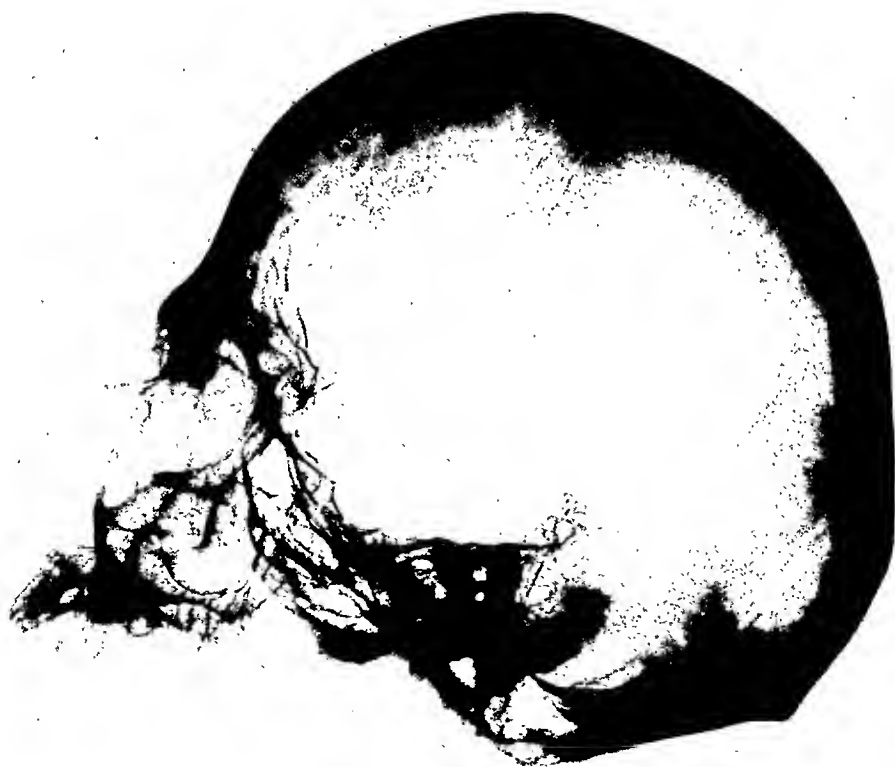


FIG. 24



## CRITICAL REVIEW

### THE TREATMENT OF GASTRIC ULCER

By EDMUND I. SPRIGGS

THE best treatment for a disease must be founded on a knowledge of its cause. Although the circumstances in which an ulcer of the stomach arises are not yet known with exactness, observation and experiment have shown that certain conditions either predispose to ulceration or tend to prevent healing.

The type of ulcer that occurs singly or in small numbers is usually painful, is independent of any recognized infectious disease, and is found only in that part of the digestive canal which is exposed to the gastric juice. The natural lining of this region, that is, of the stomach and duodenum, is normally capable of resisting the action of gastric juice, though, as Claude Bernard and Pavy showed, other tissues are not. Katzenstein (26), by a number of plastic operations, has demonstrated more recently how organs such as the spleen and jejunum are digested in the stomach even when their circulation is intact, but not the duodenum and stomach, whose resistance is attributed to the presence of an antipepsin: antipeptic activity is, however, according to Wolff and Hirsch, as strong in the juice from patients with ulcer of the stomach as in that from normal stomachs, so that ulcers do not appear to arise because antipepsin is absent.

After simple excision of a piece of mucous membrane healing takes place rapidly, as Pavy found; to produce an ulcer the edges of the excised area must be held apart mechanically and the raw surface exposed to gastric juice of high acidity (Matthes); or necrosis of an area of mucous membrane must be caused, as by the injection into the walls of the stomach of a fluid which is poisonous to its lining membrane, the gastro-toxic serum of Bolton (5).

Gross injury cannot be looked upon as a usual antecedent of gastric ulcer in man; small areas of necrosis may, however, arise from bacterial infection. Türk produced ulcers experimentally by giving *B. coli* by the mouth in increasing doses to dogs; after omitting the bacilli for a few days and then giving a dose again, symptoms ascribed to anaphylaxis appeared and peptic ulcers were found. It has long been known that in severe local or general infections multiple ulcers may be found, and may be the source of dangerous bleeding after operations. J. Hutchinson has described and collected a number of such cases. Now the ordinary gastric ulcer is found in patients who are not the subjects of any obvious general

infection; but the symptoms of ulceration are commonly preceded by those of dyspepsia. S. Martin pointed out that ulceration occurs most frequently in that part of the stomach which does not secrete acid disinfectant fluid, and ascribed its origin to a small necrotic area, resulting from infection of a gland or a lymphoid follicle. C. H. Miller gives further support to this view from histological examination of healthy, dyspeptic, and ulcerated stomachs. In the healthy stomach an erosion or loss of superficial tissue would be speedily closed by contact of the neighbouring redundant mucous membrane, as in the experiments of Pavy and Matthes. In the dyspeptic stomach he found more fibrous tissue underlying the mucous membrane, with consequent loss of mobility, and an excess of lymphoid tissue in proportion to the glandular, especially at the pylorus and along the lesser curvature. He concludes that in the formation of an ulcer an enlarged lymphoid follicle is infected, and forms a small abscess which bursts; owing to the disproportion between the lymphoid and glandular tissue, or perhaps because a number of adjacent follicles are similarly affected, the mucous membrane does not close up the lesion, with the result that the base of the little abscess is digested and the submucous layer exposed, its vessels becoming thrombosed or eroded: the surrounding inflammation favours the enlargement of the ulcer by lessening the contracting power of the muscular layer, as was shown experimentally by Schmidt (52).

We know that in the small intestine also the lymphoid patches are vulnerable areas, becoming the seat of the typhoid ulceration. If the origin of gastric ulceration in lymphoid follicles be accepted, something is done to explain the greater liability to the disease of young adults, who have reached an age at which dyspepsia is frequent, whilst the lymphoid tissues, which suffer partial atrophy later in life, are still abundant. A prolific source of bacteria is to be found in the decayed teeth and general sepsis of the mouth which often accompanies gastric ulcer.

The fact, already mentioned, that ulceration of this type only occurs in the area of peptic digestion shows that the gastric juice plays an active part in forming the ulcer and probably in delaying its healing. In support of this Bolton (6) found that if peptic action was arrested by neutralizing the juice an ulcer failed to appear even after an area of mucous membrane had been destroyed by the injection of gastro-toxic serum; whilst in the presence of normal gastric juice a damaged area became an ulcer, even though its cells had not been actually killed by the serum. Ulceration was also more easily brought about in the digesting than in the resting stomach.

The degree of acidity of the gastric contents affects the formation and healing of ulcers. Thus in Matthes's experiments an ulcer was not produced until a 0.5 per cent. solution of hydrochloric acid was left in the stomach. Bolton (6) also found that gastro-toxic ulceration was more extensive if the juice was hyperacid. Hyperacidity has been said to be a common or even a usual antecedent of ulceration. It is frequently present after the ulcer has been formed, but by no means always. Wolff, in 382 determinations after a test meal,

found the total acidity greater than 60 in 202, or 53 per cent. Out of 275 cases in which the free acid was established, in 21 per cent. the value was over 50, and in 38 per cent. over 40. Wolff quotes a number of figures from other observers:—Ewald found hyperacidity in 34 per cent., Schneider in 19 per cent., and Wirsing in 43 per cent.; Rüttimeyer found total acidity increased in 42 per cent., and excess of free hydrochloric acid in 38 per cent.; Rheinwald gave 65 per cent. as the proportion of cases with hyperacidity. But W. H. Willcox, in a series of cases in which the presence of an ulcer was proved by subsequent operation, showed that the proportion of active hydrochloric acid is nearly always high in acute ulcers. The percentage of hydrochloric acid in the gastric juice as secreted probably seldom or never rises above 0.4 per cent., which may be regarded as a normal figure for pure juice, the weaker strengths commonly found being due in health to dilution or neutralization by food. The percentage in the stomach contents will the more nearly approach 0.4 per cent. the greater the amount of juice present in the stomach in proportion to the food or other material present. So that a high percentage of hydrochloric acid in the stomach contents is not to be ascribed to hyperchlorhydria, but rather to hypersecretion or to an accumulation of secretion owing to a delayed passage through the pylorus. Hypersecretion was observed by Pawlow even to three or four times the normal in an experimental cul-de-sac which was the seat of a round ulcer. The excessive flow was present during the development of the ulcer: the secretion increased when food was taken, and the increase lasted longer than in the healthy stomach.

We have but little reliable evidence as to the effect of variations in the quantity of pepsin upon the occurrence of gastric ulcer. In any series of estimations the peptic activity does not necessarily correspond to the percentage of hydrochloric acid (Wolff), but it appears that whenever hydrochloric acid is contained in gastric juice evidence of the presence of pepsin also may be obtained.

Although the experimental evidence is clear that gastric juice is an important factor in the formation of ulcers, it is equally clear that ulcers can and do heal in spite of the presence of gastric juice. Scars of healed ulcers are found in patients who have not been treated; other patients often give a history of attacks characterized by the symptoms of gastric ulcer, from which they have recovered without special treatment; and ulcers in the stomach produced experimentally either by excision of an area of membrane or by gastro-toxic serum usually heal quickly and certainly. Bolton (6) found, for instance, that the ulcers produced in cats healed equally well whether the hydrochloric acid was increased or diminished within the limits found in the human stomach, provided that the stomach emptied itself in a normal time.

Delay in the discharge of the stomach contents, however, leading to a continuous application of gastric juice and of food to the ulcer, delays healing, although in the experimental ulcer it seldom prevents healing. When an ulcer heals, the base first becomes covered with a single layer of epithelium, and from

this layer the other layers and the glands are developed later. Griffini and Vassale found that in cats fasting for four to five days and then fed on milk a denuded area was covered with a single layer of cells in eight to ten days, but if solid food was given from the first day regeneration of the epithelium was only begun by the eighth to the twelfth day. Bolton (6) found also in cats on a milk diet that the base of a moderate sized ulcer was covered by the twentieth day, but not so soon in the meat-fed, and he attributed the delay to the longer stay of meat in the stomach, a conclusion which he proceeded to verify by constricting the duodenum in cats (7). The result of the series of experiments was that whilst an ulcer in a stomach with a normal outlet was covered with a single layer of cells in eight to ten days, and showed regeneration of the duct epithelium in 16 days, if the pylorus was obstructed these periods became 41 and 52 days respectively. It will be noted that the delay is in the establishment of the single layer of epithelium, for when the ulcer is covered over the regeneration of the duct epithelium follows nearly as soon as in the unobstructed stomach. Impediments to the growth of mucous membrane over the ulcer appear to be either the presence of necrotic tissue over the ulcer, due presumably to digestion by gastric juice, or fibrosis of the base. The presence of necrotic tissue was observed in several meat-fed animals. This artificial motor insufficiency did not prevent healing, but only postponed it; neither did the ulcers extend. The delay must not be attributed entirely to the action of acid gastric juice upon the ulcer, for the contents of the dilated stomachs were often alkaline or neutral: in such cases the ulcer would be in contact with plentiful bacterial poisons. The chronic peptic ulcer following subdiaphragmatic section of the vagi, produced by van Yzeren, was shown by him to be due to increased tone of the pylorus.

Chlorosis is to be regarded as a predisposing cause of gastric ulcer probably on account of the dyspepsia so common in that condition. Schmidt draws attention to a lessened motility of the stomach in chlorosis, a view which is supported by Agéron's observations with the sound. Gastric juice would then be liable to accumulate. The anaemia associated with the dyspepsia of older people is usually secondary to the dyspepsia. Anaemia from any cause is likely to hinder the healing of an ulcer. Quineke and Daettwyler found that ulcers which healed easily in normal dogs did not when the animals had been rendered anaemic by withdrawal of blood.

From a consideration of the experimental work we may conclude that chronic gastric inflammation with the accompanying overgrowth of lymphoid tissue, particularly when associated with oral sepsis and anaemia, predisposes to gastric ulcer; that acute ulcers tend to heal spontaneously; that healing is postponed by delay in the emptying of the stomach, leading to the continued application to the ulcer of gastric juice or of putrefying matter, and by anaemia.

We may now proceed to review the clinical methods advocated for the treatment of gastric ulcer.

Upon one point authorities are unanimous, namely, that the patient must be in bed. *Rest* was insisted upon by Cruveilhier, and practised and taught by Wilson Fox, Foster, and Williams. The period of rest in bed advised varies, as we shall see, considerably, the minimum being about fourteen days. Authorities are also agreed that the ulcer should be protected from all harmful influences such as movement of the stomach and irritation by food or by gastric juice; but there is not agreement as to how this protection can be best afforded.

We must remember that cases of gastric ulcer differ widely in character. There are two great classes of the disease, the acute and the chronic. Acute gastric ulcer, if brought under suitable treatment without too great delay, is in most cases an easily curable disease, comparable with the ulcers produced experimentally in animals, which, as we have seen, tend to heal spontaneously, even under adverse conditions. Chronic gastric ulcer, on the other hand, is often extremely resistant to treatment, though fortunately it is less common than the acute form. Between typical cases of the acute and the chronic type are all manner of grades. It follows that as regards rest or any other measure which the physician may apply success will depend upon the adaptation of the treatment to the particular case.

Many cases with haemorrhage in young women recover so quickly and so completely that it has been doubted whether they are the subjects of gastric ulcer. Donald Hood in 1892 wrote a paper expressing the view that 'the haematemeses of early adult female life need not necessarily be due to ulceration of the stomach, but . . . is possibly the result of venous congestion or stasis in the vessels of the oesophagus or stomach'. In 1906 Hale White collected a number of cases, including eight in which no lesion was found after death to explain the haemorrhage, and called the condition gastrotaxis. Apart from the multiple erosions occurring in a number of toxæmic states it cannot be said that the existence of gastrotaxis is proved; for it is very easy to miss a small acute ulcer post mortem; indeed, an almost microscopic lesion may erode a vessel and cause profuse haemorrhage, and yet such a lesion must be regarded from the points of view of pathology, symptomatology, and treatment as an ulcer. Miller's work above referred to makes it likely that acute ulcers arise from such small lesions; the difference between gastrotaxis and gastric ulcer would then simply depend upon what stage the ulceration had reached when a vessel was opened by it. The calling of attention to gastrotaxis has, however, done a service in stimulating observers to make an exhaustive examination of the mucous membrane in cases dying after haematemeses.

In discussing the various dietetic methods employed I shall, in order to give a complete view of the treatment, mention the medicinal or other measures used at the same time by the physicians who may be referred to, although medicines will also be separately discussed later in the article.



*Dietetic Methods.*

The method of temporary starvation, with or without nutrient enemas, followed by a gradual milk diet is founded on the principle that if no food is taken by the mouth absolute rest will be afforded to the stomach, rest being as conducive to the healing of an ulcer in the stomach as of a bone in the leg. If the principle is carried out logically no fluid, not water nor ice, should be given by the mouth, for, as Rolleston (47) points out, water is passed on from the stomach to the intestine, involving peristaltic movement of the stomach wall, at all events in the horizontal position. Rectal injections of ten to twenty ounces of water at 100° F. are given four times in the day.

Authorities vary as to the length of time that the patient should be prevented from taking food by the mouth. Dreschfeld advised ten to fourteen days if water injections only are being given. A well-nourished patient, as many of the subjects of gastric ulcer are, will bear deprivation of food for this period or even longer, but it should not be advised for a thin person. But for any longer time than two or three days nutrient enemas are usually supplied.

The metabolism experiments of Ehrström, Zehmisch, Bial, and Boyd and Robertson, have shown that sugar, peptone, and the fat of the yolk of egg or of milk, are absorbed in a fair proportion from the bowel, but albumin and globulin only in a slight degree. Grape sugar is better absorbed than cane or milk sugar, and absorption is aided if these foods are conveyed in 1 per cent. salt solution. Boyd and Robertson, as a result of their observations and those of others, recommend an enema of the yolk of two eggs, one ounce of pure dextrose, eight grains of common salt, and peptonized milk up to ten ounces. This amount is retained if run in slowly three times a day, the bowel being washed out with normal saline solution once a day. The three enemas have a caloric value of 900 calories, and of this absorption may take place to the extent of between three and four hundred calories. A woman of average weight lying in bed uses about 1,250 calories of energy in a day, so that enemas cannot be expected to furnish more than a third of the requirements of the body. This third is valuable, however, and may be expected to prolong greatly the length of time for which deprivation of food by the mouth can be borne. Dreschfeld recommended that the enemas might be continued for about three weeks, but that exclusive rectal feeding should not be continued beyond ten or perhaps fourteen days.

The first food to be given by the mouth is milk in quantities of two ounces every two hours, for nine doses in the twenty-four hours: it may be diluted with water, barley-water, or lime-water in the proportion of two of milk to one of the diluent. Most physicians who employ this method give food earlier if there has been no hæmorrhage.

In the absence of pain the milk is gradually increased until four to six ounces are taken at a time, and three to four pints in the day. It should not, at all events on theoretical grounds, be peptonized, for there is no difficulty in the

digestion of casein in the adult intestine, nor is it known to irritate the stomach, whereas albumoses and peptones are irritating if present in any quantity. As soon as the patient can bear a fair quantity of milk without pain rectal feeding is discontinued. The diet is then gradually increased.

We may take H. P. Hawkins's account as an example of the way in which food is added, although he does not recommend deprivation of food by the mouth for more than a few days. Some casein preparation is first given with the milk, and about a fortnight after the mouth-feeding was begun such foods as arrow-root, bread and milk, rusks and milk, cornflour, Benger's food, or thin bread and butter, two pints of milk being still taken in the twenty-four hours. At the end of four weeks, if there is no discomfort, two or three eggs are allowed, with bread, rusks, sago, tapioca and potato purée, milk soup, mutton broth, and beef tea. This diet of milk, eggs, carbohydrate, and fat is maintained for a further fourteen days. Hawkins believes that extra days spent upon it mean an increased chance of sound and permanent healing. Fish and chicken are not taken until at least six weeks after the beginning of mouth-feeding, the patient being now allowed up during part of the day. If no discomfort follows, the diet is then varied; any article of food which gives pain or discomfort being, of course, at once withdrawn. An ordinary diet, containing meat and vegetables, is postponed until the patient has shown that she is capable of digesting other foods perfectly, while carrying out her usual duties.

I do not know of any really large series of published cases treated by this method in its entirety: unfortunately the pressure on beds of hospitals is so great that it is difficult to keep patients in two or three months as a routine, even if they were willing or able to stay. Dr. Hawkins tells me, however, that a good proportion of the 556 cases, a review of which he published with Mr. Nitch, were subjected to this regime, and most of them were dieted on similar though not identical lines, especially as regards the important matter of length of stay in hospital, which they estimate roughly at an average of four weeks only.

The 556 cases admitted to St. Thomas's Hospital included 77 cases of general peritonitis from perforation, of which 47 died; 15 cases of perforation with local peritoneal infection, of which 11 died; and 45 cases suffering from sequelae of gastric ulcer, of which 11 died. Including all these the total mortality was 13.3 per cent. In 419 cases of simple ulcer the mortality rate was 1.2 per cent. The mortality during treatment is low, as we shall see, in all series: but, as Hawkins and Nitch point out, a proportion of the cases, which they put at about 10 per cent., is readmitted subsequently on one or more occasions on account of recurrence of symptoms, and an unknown further proportion is treated at other institutions or at their homes. The death-rate from haemorrhage was low, namely, less than 1 per cent. of 419 cases of simple ulcer, and 0.7 per cent. of 556 cases of simple ulcer, perforated ulcer, and their sequelae.

The practice of withholding food by the mouth for a week or more has been the subject of much discussion: it is founded upon an argument which deserves great respect, namely, that complete rest is thus given to the stomach. In well-nourished patients the starvation or semi-starvation can be easily borne. Thirst is often distressing, however, even though saline fluid be injected into the bowel. In thin women, reduced by haemorrhage or a long period of low diet or both, it must be admitted that a further abstinence from food is harmful to their nutrition, increasing the anaemia and necessitating a protracted convalescence after the ulcer is healed. Parotitis has been observed many times and almost always in patients taking no food by the mouth. It is to be attributed to a direct infection from the mouth and occurs in spite of antiseptic mouth washes. Rolleston and Oliver refer to 23 cases of which 21 were taking nothing by the mouth and the remaining two, on rectal feeding, were allowed to suck ice only. Acidosis occurs frequently: Rolleston and Tebbs observed the diacetic acid reaction in the urine in 33 out of 38 women under treatment to whom no food was given by the mouth; the reaction usually appeared about the second or third day and disappeared at a variable time after the return to mouth-feeding. In men it appeared later and was more transitory.

It is not known whether the gastric juice is completely absent in the fasting stomach if enemas are given. Bourget, Winternitz, and Umber have reported the secretion of juice when a nutrient enema is given, the last named observing the flow from a gastrostomy wound. Ewald and Michael, however, could not satisfy themselves that there was much secretion, and thought that if it occurred it must be so little as to be negligible. If gastric juice is secreted it will be harmful to the ulcer: if it is not, it is probable, as Hawkins points out, that there is an abnormal growth of bacteria in the stomach, as there certainly is on the tongue.

The unpleasantness of enemas, whether of saline solution or of nutrient material, must be counted as a drawback to the treatment; also, what is more important, the impracticability of their successful administration when trained nursing is not available, that is to say, in most of the homes of the class which is specially liable to gastric ulcer.

On account of the difficulty and unpleasantness of rectal medication, and of the miserable condition of the patient during the period of starvation or semi-starvation, the full regime, as above described, has not been widely practised except in hospitals. These considerations cannot, however, be accepted as condemning the method if it can be shown that better results are obtained by it than by other methods.

As a matter of fact, most physicians have admitted the theoretical argument as to the advantage of keeping the stomach empty, but in favourable cases, that is to say, cases in which haemorrhage has been absent or slight, and does not recur, have allowed food and omitted nutrient or saline enemas in the course of three or four days, if pain and tenderness on pressure are absent, after which

a milk or fluid diet is persisted in for a considerable time. Beef-tea was formerly used in such a diet as an alternative to milk; but is not so much now that its poor food value has been recognized, and especially since its power of exciting the secretion of gastric juice has been known.

On the Continent the combination of a short period of rectal feeding followed by a diet gradually passing from milk to ordinary foods has met with wide acceptance, and particularly the routine associated with the names of v. Leube and Ziemssen, which will now be described.

The patients are kept in bed for from ten days to two weeks; hot poultices are applied frequently to the epigastrium, unless there is haemorrhage, when an ice-bag is substituted; and 9 ounces of Carlsbad water are given lukewarm daily in the morning on an empty stomach. Carlsbad water may be imitated by prescribing 22 grains of sodium sulphate, 12 grains of sodium bicarbonate, and 10 grains of sodium chloride to the pint of water. Patients without haemorrhage begin the diet at once, those with haemorrhage are fed rectally for three days.

The diet is arranged to give a good deal of nourishment with a minimum of gastric work and of irritation, and is arranged in four periods. *First period, ten days:* Small quantities of boiled milk, meat extract, soup, and unsweetened biscuits. *Second period, seven days:* Gelatinous soups, rice and sago cooked with milk, raw and lightly boiled eggs, boiled calves' brains, and boiled chicken and pigeon without fat or skin. By this time or, in favourable cases, at the end of the first period, the patient is out of bed. *Third period, five days:* Minced underdone beefsteak, potato soup, rice soup, and a little tea or coffee are added. *Fourth period, from the twenty-second day to the end of the fourth week:* Tender beef, roast chicken and pigeon, well-cooked venison or partridge, macaroni, and a little white bread are now allowed. From the fifth week on, a return is gradually made to ordinary food.

Under this plan of treatment the patient is taking a nourishing diet in a fortnight. v. Leube has reported the treatment of 627 cases in the last eleven years with a mortality of 0.3 per cent. Of these, 90 per cent. are classified as well on giving up treatment, 8.5 per cent. as improved, and 1 per cent. as unimproved. In v. Leube's earlier series the mortality was 2.4 per cent.

There is difference of opinion, as we have seen, as to when to begin the mouth-feeding. It is clear that no rule of thumb will serve here, for neither patients nor their diseases are cut to one pattern. If haemorrhage has been recent, and if the physician takes the view that any food in the stomach is likely to cause a recurrence until the wounded vessel is soundly sealed, his practice should be to give no food by the mouth until all evidence of blood in the faeces is gone. Small leakages may be detected by the tests for 'occult' blood. The benzidine test is the most sensitive. Dr. Buckmaster has kindly recommended to me the following method of applying the test:—A knife-point of benzidine is

dissolved in 3 c.c. of glacial acetic acid, and to this a watery extract of faeces, which has been boiled, is added in the proportion of 3 or 2 parts of the solution to 1 of the extract. Then mix and add 2 c.c. of 3 per cent. peroxide of hydrogen and allow to stand. A colour, green to blue-green, develops according to the amount of blood present; if a good deal, at once, if little, in a few minutes.

The point in v. Leube's routine which is perhaps open to most criticism is the short time of rest in bed. Most physicians are agreed that there should be complete rest for longer than ten days or a fortnight, and many will agree with Schmidt when he says that rest in bed is more important than all other measures.

Ewald follows a similar plan, but has given up poultices without recognizing any disadvantage, and does not prescribe a daily draught of Carlsbad water, relying on an enema every second or third day to open the bowels. Neither of these measures has found great favour in this country, although, in the absence of haemorrhage, a poultice will often relieve pain and obviate the necessity for an opiate in the early days of rest in bed. The exact diet taken for the first fortnight by a patient progressing favourably is set forth in the following scheme. The table is taken from the recent paper by Wolff in which Ewald's methods and results are described fully. The quantities are translated into Imperial measures:—

TABLE I.

Day of Treatment.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Nutrient enemata . . .	3	3	3	2												
Cream, oz. . . . .											7	7	7	7	7	7
Milk, oz. . . . .				16	25	25	36	50	54	54	46	46	46	46	72	72
Eggs . . . . .					1	2	3	5	5	5	5	3	2	2	4	4
Soup, oz. . . . .								4	4	10	18	18	18	10	10	10
Minced ham, oz. . .								1	1	1	1	2	2	3	3	3
Minced veal, oz. . .									2	2	2	2	3	3	2	3
Biscuits (number) . .											3	3	3	5	6	6
Gruel of oatmeal or rice, oz. . . .										3	3	4	4	4	4	7
Mashed potato, oz. .												4	4	4	4	4
Vegetables (spinach), oz. . . .																2
Calories . . . . .	400	400	400	581	561	632	913	1465	1535	1668	2083	2176	2105	2132	2350	2380

The enema used by Ewald consists of nine ounces of milk, two eggs, a drachm and a quarter of Tropon (a preparation containing a mixture of vegetable and animal protein), a knife-point each of salt and sugar, and a few drops of tincture of opium. As has been shown above, such knowledge as we have of the absorption of food from the bowel leads to the conclusion that the enema would not lose in value if the white of the eggs and the Tropon were left out, whilst more of it would be absorbed if the milk were thoroughly peptonized. More sugar

might be added with advantage. Wolff remarks that the psychical effect of the enema is good, from which we may perhaps conclude that it is not supposed to furnish much energy to the body. Acute parotitis is not reported in patients kept on enemata for three days only.

Wolff's paper refers to 700 cases treated by Ewald. Complete recovery was attained by 48.8 per cent., improvement in 31.6 per cent., 13.2 per cent. were passed on to the surgeon, 4 per cent. were no better, and 2.3 per cent. died. The value of these results turns upon what is meant by improvement. We shall see later that in an inquiry into after-results it appeared that 55 per cent. of the patients remained free from pain or dyspeptic symptoms of any kind. Ewald's experience, agreeing with that of other observers, is that a better prognosis can be given in cases of hæmorrhage, than in those free from that symptom: probably the alarm accompanying a loss of blood contributes much to the thoroughness with which the treatment is carried out, especially as regards complete rest on the part of the patient. Hæmorrhage is also often, though not always, evidence of the acuteness of the ulceration, and acute ulcers heal much better than chronic ones. Out of 652 of Ewald's cases 11 died from hæmorrhage. One had lost but little blood, but suffered from fatty degeneration of the heart. Two others were operated on unsuccessfully. If these three are excluded the deaths from hæmorrhage are reckoned at 1.2 per cent.

Weintraud has followed the Leube regime on the whole, but omits the Carlsbad water and does not allow a patient to get up until she can take a mixed diet without any pain, a regulation of the highest value. He reports a series of 133 cases with no death: two-thirds of the cases suffered from hæmorrhage. He records his impression that the large doses of bismuth now given are beneficial. A similar plan of treatment has been recommended by Saundby for many years; in 1891 he advised, in cases of hæmorrhage, rectal feeding for a day or two followed by equal parts of milk and lime-water in ounce doses every hour. Then bread and butter and custard were given, and later eggs and pounded chicken, the patient being led to a full nourishing diet as soon as possible. An iron pill and magnesia were ordered to be taken daily.

In all the above-mentioned methods of treatment nutrient or saline enemata are administered for a longer or shorter time, if not in all cases, in those with bleeding from the ulcer. The majority of patients with gastric ulcer in private practice, however, do not receive rectal feeding, for this is only practicable when some form of skilled nursing is available, whereas the disease is commonest among young women of the poorer classes. Probably most practitioners follow the plan of starving the patient for two or three days, allowing a little ice to suck, or sips of feed milk or water, and begin regular feeds of milk about the third day, which are increased until the patient is taking three pints in the day. After this the milk is thickened, custard and eggs are added, followed by soups, bread and milk, milk puddings and fish. Meat is left till last. The presence or

absence of pain after food is taken is the chief guide in prescribing the diet from day to day. We have no means of estimating the percentage of successes obtained by this treatment, from any published figures, but it may be said that though gastric ulcer is a common disease death from gastric ulcer is not common.

Neither have nutrient or saline enemas received acceptance in all hospitals. Dr. F. J. Smith informs me that the treatment he prescribes at the London Hospital is as follows:—For the first twenty-four hours water only is given. The patient is then allowed three small meals in the day, not milk alone, but milk and arrowroot, soup or beef-tea, followed by boiled egg, bread and butter, and a cup of tea. In five or six days minced fish is allowed, the duration of treatment being a fortnight to three weeks. The same routine is followed whether there has been bleeding or not. We cannot judge of the ultimate success of this routine as the figures recently quoted by Dr. Smith refer to patients in the hospital under different physicians. Of 606 cases treated medically in the years 1899–1908 the mortality was 9.4 per cent. Of 314 cases treated surgically in the years 1903–7, excluding perforations, the mortality was 17 per cent. Many of the surgical cases were severe cases in which medical treatment had failed. The death-rate in large institutions is likely to be higher than in series treated by only one man. The London Hospital is also in a very poor district, and among the most ignorant classes patients are often not brought to hospital until their state is serious. Of the 606 cases treated medically relapse was known to occur in 12.3 per cent., and of the 321 cases treated surgically in 8.9 per cent. The figures include gastric and duodenal ulcers in the proportion of about ten to one.

In 1901 Lenhartz of Hamburg made a new departure in the theory and practice of the treatment of gastric ulcer. His treatment is founded on the propositions that the presence of semi-solid food in the stomach is not so harmful to an ulcer as that of gastric juice without food: that gastric juice is not entirely absent in the fasting stomach, and in addition to irritating an ulcer may cause recurrence of haemorrhage by dissolving a clot: that the subnutrition accompanying rectal feeding and a milk diet is prejudicial to the healing of an ulcer. The experimental observations of Matthes, Quincke, Umber, and others referred to above, are quoted in support of these propositions. An essential point of the method is that the food introduced into the stomach shall be of such a nature as to excite but little flow of juice, and to neutralize the hydrochloric acid of any that is secreted; also there must always be some food in the stomach in the waking hours, but never enough to distend it. For this purpose teaspoonful doses of beaten-up egg and milk are prescribed. Egg albumin rapidly combines with hydrochloric acid. Milk calls forth less secretory activity in the stomach than any other food. The fat of the yolk of egg and of the milk is known to inhibit the secretion of juice. Nothing else but milk, egg, and a little sugar is allowed for five days. As the food is given in such small quantities the

movements of the stomach are reduced to a minimum. Experiment shows, as we have seen, that distension of the stomach, by keeping the mucous membrane from closing over an ulcer, is likely to be far more harmful than contraction. The feeding is begun within a few hours of hæmorrhage.

The general routine of the treatment advised by Lenhartz is as follows:—The patient is kept absolutely in bed for four weeks, for the first two of which she is not allowed to move from the supine position for any reason whatever. All mental excitement must be avoided. An ice-bag is kept upon the stomach almost continuously for the first two weeks. The dietary consists of eggs beaten up with sugar, or in some cases with wine, and iced; and of milk. These two foods are taken in small quantities at frequent intervals from a teaspoon, the quantity prescribed being spread over the day, and not given at definite meal-times. The first day 7 to 10 ounces of milk are given and one egg. The quantity is increased daily by  $3\frac{1}{2}$  ounces of milk and one egg until  $1\frac{3}{4}$  pints of milk and six eggs, or in some cases eight eggs, are reached. If there is any pain or distension the quantity of milk is reduced. From about the third to the eighth day raw, or almost raw, mince is added, starting with an ounce in divided doses, either beaten up with the egg or alone; the next day, if the mince is well borne, 2 ounces are given. From the seventh to the eighth day boiled rice is added, followed by softened bread and later by a small quantity of bread and butter. One or more eggs may now be lightly boiled. The diet is then gradually increased by the addition of meat or pounded fish, with a corresponding reduction of eggs, until by the end of the fourth week the patient is on an ordinary mixed diet containing the common food-stuffs with the exception of indigestible solids such as peas and other seeds. The patient is instructed to masticate very slowly. On the twenty-eighth day the patient is allowed to get up, and discharged from the sixth to the tenth week. For the first ten days bismuth subnitrate is given in doses of 30 grains in water without mucilage twice or three times a day. From the sixth to the tenth day sulphate of iron is prescribed in the following form:—

Sulphate of iron	. . . . .	150 grains.
Calcined magnesia	. . . . .	20 "
Glycerine	. . . . .	1 drachm.

Mix and divide into 60 pills.

Two of these are given two or three times a day. Lenhartz increases the dose gradually, giving three for three days, four for four days, up to ten for ten days, and then down again. In some cases arsenic is added. The bowels are not disturbed at all during the first week unless they are naturally opened. An enema is then given and repeated every fourth day during treatment. The mouth should be washed out and attended to regularly.

The following table shows a typical diet for the first fortnight; the quantities are given in Imperial measures.



TABLE II.

Days after last haemorrhage.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Eggs . . . . .	2	3	4	5	6	7	8	8	8	8	8	8	8	8
	beaten up						4 beaten up 4 lightly boiled				maximum			
Sugar added to eggs, oz. .			$\frac{3}{4}$	$\frac{3}{4}$	1	1	$1\frac{1}{2}$	$1\frac{1}{2}$	2	2	2	2	2	2
Milk, oz. . . . .	7	10	14	18	21	25	29	32	36	36	36	36	36	36
	in spoonfuls													
Raw mince, oz. . . . .						1	2	2	2	2	2	2	2	2
Rice boiled in milk, oz. .							4	4	7	7	10	10	10	14
Biscuits (of $\frac{3}{4}$ oz. each) .								1	2	2	3	3	4	5
Raw or underdone meat, oz.										2	2	2	2	2
Butter, oz. . . . .										$\frac{3}{4}$	$1\frac{1}{2}$	$1\frac{1}{2}$	$1\frac{1}{2}$	$1\frac{1}{2}$
Calories . . . . .	280	420	637	777	955	1135	1588	1721	2138	2478	2941	2941	3007	3073

As regards the features of the later treatment, it is to be noted that a month's rest in bed is ordered, and a further month or six weeks under observation. No patient is regarded as cured until not only have all symptoms vanished, but the motions have been free from blood for several weeks, and the haemoglobin percentage is raised to a normal figure.

In 1909 Lenhartz reported 295 cases, of which 262 had suffered from severe bleeding. Seven died, a mortality of 2.3 per cent. After the publication of the first 60 cases treated on this plan (Wagner) a chorus of caution arose condemning the putting of food into a stomach which had recently bled. The criticism appears weighty, but when John Hunter's principle is applied it loses much of its force. Indeed several observers now report that the method of immediate feeding gives more favourable results in cases of haemorrhage. Wolff, after a critical correction of the statistics of Lenhartz's series of 295 cases, and Ewald's of 652 cases, concludes that the mortality from haemorrhage works out at 1 per cent. and 1.2 per cent. respectively. It is an interesting sign of the change of opinion following on the extensive trial of immediate feeding that Wolff is concerned rather to defend Ewald than to attack Lenhartz, for he remarks that the figures show that abstinence from food is not more dangerous than feeding. Minkowski in 1905 reported favourably of the method, which he had used in 30 cases.

Wirsing reported 42 cases in 1906, 14 of which had had recent haematemesis. In one case haemorrhage recurred. In 27 of these patients the acidity of the stomach contents was estimated: it was found that during the treatment the amount and percentage of hydrochloric acid were diminished, the latter falling on the average from 0.14 to 0.11 per cent. Some cases did not show this, and yet progressed as well as the others.

Lambert in 1907 published 5 severe cases, all of whom did well on the treatment. One was a woman of thirty-two years, who, after seven days' rectal feeding and seven days' careful feeding by the mouth with peptonized milk, still had occult blood in the stools and a haemoglobin percentage of 39, and the

question of operation was being mooted. The Lenhartz treatment resulted in a cure. Another patient objected to the diet, even to the point of nausea and vomiting, but, nevertheless, after the cessation of the diet for one day, did well. In another haemorrhage went on until the thirteenth day, and the case was regarded as below the safe limit for surgery, and yet made a good recovery on this treatment. A fourth case with signs of peritoneal irritation, leucocytosis, and a temperature of  $100^{\circ}$  to  $104^{\circ}$ , also recovered. In a fifth case, in which the haemoglobin was reduced to 20 per cent., in spite of an attack of enteric fever upon the twenty-second day, the treatment proved successful.

A trial of the method was made by myself in 1906 (58, 59). From a comparison (57) of 33 cases with haemorrhage treated in St. George's Hospital by this diet with 34 cases treated by other methods, the conclusions were drawn that the Lenhartz method of treatment is not more dangerous than treatment by nutrient and saline enemata followed by a graduated milk diet; in these particular cases it was found that the recurrence of haemorrhage was less frequent and there were no deaths: that the pain suffered by the patient in the course of treatment is less on the Lenhartz diet: that the diet gives far more nourishment than can be introduced into the body by nutrient enemata, and is, therefore, desirable in patients who have frequently been for a long time in a state of semi-starvation, or have suffered a loss of blood, or both. In my cases the mincemeat was lightly cooked, the carbonate or oxychloride of bismuth was substituted for the subnitrate, and the iron pill was not given more than three times a day.

Langdon Brown has reported favourably of his experience of the diet.

Mayerle reports 71 cases, of which 29 had suffered from recent haemorrhage. He replaced the raw mince by cooked mince, and gave some such food as Hygiama<sup>1</sup> instead of the last four eggs. In no case did he think any harm was done by the feeding. Healing took place in 86 per cent., in 65 per cent. straightforwardly, in 11 per cent. more slowly, and in 10 per cent. after relapse. In 3 cases there was some recurrence of bleeding. In 10 per cent., 7 cases, the treatment did no good, and 7 per cent., 5 cases, could not endure the diet. He speaks well of the treatment, but recommends that more fat should be added to the diet in cases of hypersecretion, and that in chronic cases with but little secretion less protein should be given, with an increase of both fat and carbohydrate.

Weintraud admits that Lenhartz's method of treating bleeding ulcers is now justified by results at least as favourable as are obtained by v. Leube's method, 2.3 per cent. of deaths as compared with 2.5 per cent. He finds, however, that in cases marked by much pain after food, milk and thin soups, with some farinaceous food such as Mellin's, Nestlé's, or Hygiama, are more successful in arresting the pain; morphine or codeine must sometimes be used as well. Lenhartz, on the other hand, says he does not find that any opiate is

<sup>1</sup> Hygiama is a milk food with the addition of meal and cocoa butter. In general composition it resembles Allenbury No. 1 and John Bull No. 1 Foods, but it contains some uninverted starch. Maltico and Nutroa are also similar foods

needed by his patients. If vomiting is severe, and especially if blood is brought up, Weintraud prefers abstinence and morphia to giving any food, but only for about twenty-four hours. He fears that the success of the Lenhartz method may lead to its becoming too rigidly followed.

Lenhartz claims that, owing to the protection afforded to the newly-formed thrombus by the neutralization of the gastric juice by the protein of egg and milk, recurrences of haemorrhages are less frequent in patients under his treatment than in others. He quotes some remarkable instances of patients who had bled repeatedly in whom the bleeding ceased immediately feeding was begun. I have published a case of this kind (56) in which seven large haemorrhages had occurred in the course of a week. The patient had been treated with morphine, an ice-bag, rectal and intravenous injections of saline solution, horse serum, and adrenalin. She was in an extreme condition, the pulse scarcely palpable, in spite of continuous saline subcutaneous infusion. Operation was judged to be impracticable. Feeding with milk and eggs in teaspoon doses was begun, and there was no more bleeding, the patient making an uninterrupted recovery. The recital of such cases does not prove that the feeding caused the improvement, because it is well known that the most remarkable recoveries after bleeding are seen. It does seem clear, however, that the feeding did not predispose to further haemorrhage, and the rapid increase in the energy value of the food must be of great advantage to an impoverished, anaemic patient.

Elsner, whilst supporting the principle of early feeding with a diet which is non-irritant and will bind hydrochloric acid, points out that minced meat makes it impossible to test the faeces for minute quantities of blood, and thinks that eggs are unpleasant to take. He gives increasing doses of milk with Hygiama and large doses of alkali. The following are the proportions of milk, Hygiama, and sugar recommended for the first six days:—*First day*, 8 ounces of milk, two-thirds of an ounce of Hygiama, and two-thirds of an ounce of sugar. *Second day*, 11 ounces, 1 ounce, and two-thirds of an ounce respectively. *Third day*, 20 ounces, 2 ounces, and 1 ounce. *Fourth day*, 28 ounces, 3 ounces, and 1 ounce (1,000 calories). *Fifth day*, 35 ounces, 4 ounces, and 1 ounce (1,220 calories). On the *sixth day*, butter, cream, biscuit, raw or lightly cooked eggs are allowed. Three and a half ounces of Hygiama are about equal in food value to a pint of milk. Allenbury No. 1 food may, as has been mentioned, be used in place of Hygiama. Elsner gives a teaspoonful of bicarbonate of soda or of magnesia three or four times a day, but objects to an iron pill on account of its irritating properties. It may be doubted, however, whether the iron pill is as irritating as the above repeated dosage with alkali, or whether it is as good to bind the hydrochloric acid with an inorganic alkali as with fluid or semi-fluid protein, which has the double advantage of combining with acid and supplying food.

A method of immediate feeding differing in some respects from that of Lenhartz is used by Senator, who recommends teaspoon doses of an 8 per cent. solution of gelatin every hour or two, or every quarter- or half-hour if bleeding is

severe, with the object of arresting haemorrhage and sparing protein. Fat is given in the form of nine ounces of cream and an ounce of butter in the twenty-four hours. The butter may be in the form of frozen pellets which are sucked by the patient. Then milk, beaten eggs, and scraped meat are given, the gelatin being gradually left off but resumed if there is any more bleeding. If the patient can take this quantity of cream the energy value of the food is greater than that of the Lenhartz diet for the first few days, reaching 900 to 1,000 calories. Senator reported fifty cases fed in this way, of which two died, that is, 4 per cent. Weintraud criticizes this treatment, having found that gelatin by the stomach is often followed by nausea and vomiting.

In former days fatty foods came to be thought unsuitable for patients with any disease of the stomach, as being likely to cause 'bilious' vomiting. When the work of Pawlow and his school showed that fats lessen the secretion of gastric juice and begin to pass the pylorus earlier than other foods their value in hypersecretion (3) and pyloric spasm was recognized. In 1900 P. Cohnheim introduced the use of olive oil for ulcers and their sequelae, such as stenosis, hyperchlorhydria, pain, spasm, and dilatation. Oil allays irritation, lessens spasm, and keeps the bowels open: it is also a valuable food. He gave a wine-glassful an hour before the three chief meals. In 1902 Walko advised oil alone in ulcer of the stomach in doses of  $1\frac{1}{2}$  oz. to 2 oz. three times a day for three to six days, or until the severest symptoms have yielded. In a more recent paper Walko recommends a mixture of  $3\frac{1}{2}$  oz. of olive oil,  $1\frac{1}{4}$  drachms of a bismuth salt, and  $\frac{3}{4}$  drachm of calcined magnesia. An emulsion of oil, the yolk of raw eggs, and sugar is ordered as well, to be taken every three hours. On the third day cold milk is begun, followed by the diet advised by v. Leube. A fortnight's strict rest in bed is enjoined. Bone marrow is also recommended. He reports that he has treated over 100 patients in this way. If strong repugnance is shown some other diet is substituted, but this does not happen in more than one-fifth of the patients. In cases of haemorrhage an ounce of olive oil with 15 to 30 grains of bismuth is given four times in the day, iced jelly being taken between.

In this country olive oil has been chiefly used in the treatment of duodenal ulcer. A. F. Hertz has advocated it. Since recording my own impression of its value in duodenal ulcer (56) I have used it for many gastric ulcers which present evidence of being situated near the pylorus, ordering half an ounce every three hours with or without other food. About the second or third day of the administration of oil thirst may become intense, and should be relieved by repeated small doses of water. The use of olive oil may be combined with the beaten-up egg and milk of Lenhartz with advantage. Patients take it very much better than might be expected, and not a few, having once learnt its value, are loath to leave it off, even long after all symptoms have ceased. In others it may cause nausea and diarrhoea, and must be discontinued. For such Cohnheim recommended almond milk: this is the *Mistura amygdalae* of the British Pharmacopoeia, without the gum acacia and the sugar. It may be made at

home by extracting a tablespoonful of powdered sweet almonds with half a pint of boiling water and squeezing through muslin. A wineglassful is ordered lukewarm an hour before the chief meals, the patient lying on the right side for a while after taking it. The beneficial influence of fat is recognized in most of the diets mentioned above, in which butter and cream are prescribed freely, and especially in those recommended by Senator and Ewald.

In a comparison of the various dietetic methods v. Leube's latest series appears to stand first of the large groups statistically. The proportion of bleeding cases was, however, small, giving rise to the suspicion that many of the cases were mild ones, especially as the figures include private patients. The results in practice among the well-to-do are far better than in hospital patients, as is to be expected. The St. Thomas's Hospital series, compiled by Hawkins and Nitch, showed excellent results in cases of simple ulcer. The figures include the mortality from all causes in both medical and surgical cases and are an example of what such statistics should be.

It is clear that simple ulcer may be successfully treated by very different methods. The physician will be wise not to confine himself too closely to one or the other. An advance is marked by the demonstration in recent years of the value of immediate feeding with protein and fat, and of fat alone.

Good after-results cannot be expected unless the patient is kept under treatment until there is no anaemia.

The fact that an ulcer may be covered completely with a single layer of epithelium in eight days or so, provided that necrotic tissue does not cover its base, suggests that whatever plan be adopted to prevent the action of gastric juice upon an ulcer should be persisted in for that time at least. For instance, foods stimulating secretion, such as soups or mincemeat, should on this ground be withheld longer than is advised by v. Leube and Lenhartz respectively.

### *Medicines.*

Bismuth holds the first place in the treatment of ulcer, the tendency being to give it in larger doses than formerly—for instance, not less than half a drachm, and often a drachm at a dose. It is better not to suspend it with mucilage, because if it is suspended in the bottle it will be suspended in the stomach, whereas it is intended to form a coating of powder over the mucous membrane and especially over the ulcer. The subnitrate has occasionally been known to cause symptoms of gastric irritation, attributed to the formation of nitric acid and nitrites. It is better to use, therefore, the carbonate or the oxychloride. The carbonate will be more efficient in neutralizing acid gastric juice, but on the other hand some carbon dioxide gas will be evolved, so that the oxychloride is probably the best preparation. The liquor bismuthi contains too little bismuth to be of great value.

Aluminium preparations have been introduced to combine the effect of an insoluble powder, like a bismuth salt, with astringency. Escalin, recommended

by Klemperer, is an aluminium glycerin paste, of which 3 drachms are given in watery suspension immediately after bleeding, and repeated. It does not, however, appear desirable to put a hygroscopic irritating material like glycerin in contact with inflamed mucous membrane. A substance sold by Kahlbaum under the name of Neutralon is silicate of aluminium; this combines slowly with hydrochloric acid, forming inactive silicic acid and aluminium chloride. Neutralon is stated to cover the surface of the mucous membrane as an insoluble powder; when it is decomposed by hydrochloric acid the chloride of aluminium formed is astringent and disinfectant. The dose recommended, one teaspoonful suspended in 3 ounces of water, will gradually neutralize 400 c.c. (14 ounces) of 0.2 per cent. hydrochloric acid at the temperature of the body. The dose is given a quarter to half an hour before meals, and is reduced to half a teaspoonful after some days. Alexander has obtained good results by combining it with belladonna. In eighteen cases of ulcer he reports that the best effects were obtained when haemorrhage had occurred. This, however, appears to be reported whatever treatment is being applied. In the conditions of hyperchlorhydria and hypersecretion, which are believed often to be the precursors of gastric ulcer, Neutralon is said to be very effectual. It is claimed that it is much less constipating than bismuth or silver salts. Rosenheim and Ehrmann report that in two and a half years' use of Neutralon they have observed no unfavourable effects; but whilst agreeing as to its efficacy in hypersecretion, they do not think it is so good in ulcer as large doses of bismuth.

Sodium bicarbonate is a valued remedy for the relief of pain due to the irritation of an inflamed mucous membrane or of an actual ulcer by the acid juice. It is added to milk in the proportion of two grains to the ounce with advantage. It may, however, be doubted whether repeated dosage with alkali in such strength as is recommended by Elsner, namely, a teaspoonful three or four times a day, is beneficial to the mucous membrane or to the ulcer, especially as much carbon dioxide gas is formed. It is probable that large doses of alkali are only advisable when given at a definite time after an ordinary meal to neutralize an accumulation of gastric juice, as in cases of pyloric or duodenal ulcer.

Magnesia may be used for the same purpose, and has the advantages that it does not give off carbon dioxide, and that when it has left the stomach it acts as a purgative. My own experience is that it is more irritating to the stomach than bicarbonate of soda.

Silver nitrate has been used for its astringent effect, a quarter of a grain being given in solution. Dreschfeld advised it for patients who cannot rest in bed.

Atropine is recommended to lessen both the movements and the secretion of the stomach. Drop doses of the *Liquor atropinae sulphatis* are ordered in a mixture, or  $\frac{1}{1000}$  grain may be given hypodermically three times a day.

Iron is almost always prescribed at some period: Lenhartz orders a soft Blaud's pill throughout, but most physicians prescribe it after the ulcer appears,

home by extracting a tablespoonful of powdered sweet almonds with half a pint of boiling water and squeezing through muslin. A wineglassful is ordered lukewarm an hour before the chief meals, the patient lying on the right side for a while after taking it. The beneficial influence of fat is recognized in most of the diets mentioned above, in which butter and cream are prescribed freely, and especially in those recommended by Senator and Ewald.

In a comparison of the various dietetic methods v. Leube's latest series appears to stand first of the large groups statistically. The proportion of bleeding cases was, however, small, giving rise to the suspicion that many of the cases were mild ones, especially as the figures include private patients. The results in practice among the well-to-do are far better than in hospital patients, as is to be expected. The St. Thomas's Hospital series, compiled by Hawkins and Nitch, showed excellent results in cases of simple ulcer. The figures include the mortality from all causes in both medical and surgical cases and are an example of what such statistics should be.

It is clear that simple ulcer may be successfully treated by very different methods. The physician will be wise not to confine himself too closely to one or the other. An advance is marked by the demonstration in recent years of the value of immediate feeding with protein and fat, and of fat alone.

Good after-results cannot be expected unless the patient is kept under treatment until there is no anaemia.

The fact that an ulcer may be covered completely with a single layer of epithelium in eight days or so, provided that necrotic tissue does not cover its base, suggests that whatever plan be adopted to prevent the action of gastric juice upon an ulcer should be persisted in for that time at least. For instance, foods stimulating secretion, such as soups or mincemeat, should on this ground be withheld longer than is advised by v. Leube and Lenhartz respectively.

### *Medicines.*

Bismuth holds the first place in the treatment of ulcer, the tendency being to give it in larger doses than formerly—for instance, not less than half a drachm, and often a drachm at a dose. It is better not to suspend it with mucilage, because if it is suspended in the bottle it will be suspended in the stomach, whereas it is intended to form a coating of powder over the mucous membrane and especially over the ulcer. The subnitrate has occasionally been known to cause symptoms of gastric irritation, attributed to the formation of nitric acid and nitrites. It is better to use, therefore, the carbonate or the oxychloride. The carbonate will be more efficient in neutralizing acid gastric juice, but on the other hand some carbon dioxide gas will be evolved, so that the oxychloride is probably the best preparation. The liquor bismuthi contains too little bismuth to be of great value.

Aluminium preparations have been introduced to combine the effect of an insoluble powder, like a bismuth salt, with astringency. Escalin, recommended

*Operative Treatment.*

Perforation and such mechanical conditions as pyloric stenosis, hour-glass stomach, perigastric abscesses, and adhesions should be treated surgically. In severe haemorrhage the indications are less clear, for, as has just been mentioned, the mortality in any large series of cases operated on for haemorrhage is greater than in cases not operated upon. The physician must, nevertheless, consider the matter from the standpoint of the individual case. The choice of an operation, if any be done, also presents some difficulty. Mayo Robson recommended gastro-enterostomy, but many recurrences of bleeding after that operation have been observed; indeed, for the time, it is difficult to see what gastro-enterostomy does that is not accomplished by lavage. If the bleeding area can be found it is probably better to excise the ulcer or to tuck it in and occlude the vessels in that way.

There is another class of case in which operation is of great benefit, namely, in chronic ulcers which have resisted thorough medical treatment. Gastro-jejunosotomy is the operation of choice, with excision of the ulcer, if possible, if it is indurated. It is not within the scope of this review to detail the statistics of operative procedures, but it may be said that Paterson, Mayo Robson, Moynihan, Rutherford Morison, Busch, Clairmont, and other surgeons have published series of cases showing that the mortality is low and that a large proportion of the patients remain free from symptoms. The result appears to vary with the situation of the ulcer, as we should expect: if it is situated near the pylorus gastro-enterostomy is more favourable than it is for ulcers in the cardiac half of the stomach (14). Thus Clairmont reports that in v. Eiselberg's clinic 73 per cent. of duodenal ulcers healed after operation, 62 per cent. of those near the pylorus, and 47 per cent. in the body of the stomach.

If a tumour can be felt an operation should be done and a piece excised to ascertain whether it is inflammatory or not (56); a gastro-jejunosotomy can be performed at the same time.

*After-results.*

Ulcer of the stomach is a disease that recurs, especially in young adult women. Presumably the patient is prone to ulceration so long as the predisposing causes, namely, dyspepsia, with active proliferation of lymphoid tissue, and anaemia, are in operation. The liability to recurrence becomes smaller when middle life is reached. We ought in considering after-results to distinguish between repeated attacks of an acute ulcer and the recurrence of symptoms in the subject of a chronic ulcer which was probably imperfectly healed. Unfortunately this has not generally been done. Further, owing to the disease being most prevalent among the poorer classes it is difficult to trace the patients who have been under treatment, so that the statistics of the late effects of treatment are scanty, and do not usually cover a much longer period than a year or two after the patients have left the hospital. By taking the average



of 431 cases followed up by several authors Wolff found that about 50 per cent. of the cases were permanently healed: these patients were treated either with v. Leube's or a similar diet. It is interesting to note that in Wolff's series a quarter of those who left the hospital 'unhealed' got quite well. Westphalen inquired into the state of 150 patients, each of whom had left the hospital two years or more. Of these 37 per cent. were definitely cured after one course of medical treatment, and another 16 per cent. after more than one course, 53 per cent. in all. A further 13 per cent. were healed by operation, making 66 per cent. free from all symptoms. Of 36 cases operated upon 53 per cent. were fully healed after two years, the less favourable being those cases which had resisted repeated medical treatment, and the most favourable those with some mechanical deformity, such as stenosis. The number of cases treated by immediate feeding which have been traced is too small to furnish any valuable conclusion, but the results appear to be not inferior.

Few large series of cases have yet been traced to show the after-results of gastro-enterostomy when performed for the relief of gastric ulcer. Mayo Robson states that he has obtained 101 cures out of 110 cases: but these were all in private practice and were presumably not poor people. The results are not, therefore, comparable with statistics drawn from hospital patients, who too often return to the conditions in which the disease arose. We know that ulceration may recur after gastro-enterostomy, but from Paterson's analysis of 143 cases it is probable that between 80 and 90 per cent. remain well if the patients are properly selected.

The mortality in the medical treatment of uncomplicated gastric ulcer is so low that any surgical interference cannot fail to increase it. It is in the chronic cases and those recurring frequently that we may look to gastro-enterostomy to give relief and to prevent the later complications of chronic ulcers.

#### REFERENCES.

1. Agéron, *Münch. med. Wochenschr.*, 1902, xlix. 1256.
2. Alexander, A., *Berl. klin. Wochenschr.*, 1909, xli. 2193.
3. Baekman, W., *Zeitschr. f. klin. Med.*, Berlin, 1900, xl. 224.
4. Bial, *Archiv f. Verdauungskr.*, 1903, ix. 433.
5. Bolton, C., *Proc. Roy. Soc.*, Lond., 1905, lxxiv. 135; Ser. B, 1906, lxxvii. 426; Ser. B, 1907, lxxix. 533.
6. Bolton, C., *Proc. Roy. Soc. Med.*, Lond., 1910, iii, Therap. Sect., 117.
7. Bolton, C., *Proc. Roy. Soc.*, Lond., 1910, B., lxxxii. 233.
8. Bolton, C., *Brit. Med. Journ.*, 1910, i. 1221.
9. Bourget, *Therap. Monatsh.*, 1909, xxiii. 353.
10. Busch, *Arch. f. klin. Chir.*, Berlin, 1909, xc. 1.
11. Boyd and Robertson, *Scottish Med. and Surg. Journ.*, 1906, xviii. 193.
12. Clairmont, P., *Mitth. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, xx. 330.
13. Cohnheim, P., *Zeitschr. f. klin. Med.*, Berlin, 1904, lii. 110.
14. Deanesly, E., *Brit. Med. Journ.*, 1910, ii. 956.
15. Dreschfeld, *Allbutt and Rolleston's System of Medicine*, Lond., 1907, iii. 483.
16. Ehrström, *Zeitschr. f. klin. Med.*, Berlin, 1903, xlix. 377.
17. Elsner, *Therap. d. Gegenw.*, Berlin, 1903, xlix. 55.

18. von Ewald, *Deutsch. med. Woch.*, 1908, xxxiv. 361.
19. Griffini und Vassale, *Beitr. z. path. Anat.*, Jena, 1888, iii. 425.
20. Haberman, J. V., *Lancet*, Lond., 1906, ii. 25.
21. Hawkins, H. P., *A System of Diet and Dietetics*, ed. by G. A. Sutherland, Lond., 1908, 498.
22. Hawkins, H. P., and Nitch, C. A. R., *Med.-Chir. Trans.*, Lond., 1907, xc. 339.
23. Hutchinson, Jonathan, *Proc. Roy. Soc. Med.*, Lond., 1910-11, iv, Surg. Sect., 58.
24. Hood, D. W. C., *Trans. Med. Soc.*, Lond., 1892.
25. Katzenstein, *Deutsch. med. Woch.*, 1907, xxxiii. 95 and 138.
26. Katzenstein, *Berl. klin. Wochenschr.*, 1908, xlv. 1749.
27. Kaufmann, F., *Amer. Journ. of Med. Sci.*, Philad. and N. York, 1910, N. S., cxxxix. 790.
28. Klemperer, *Therap. d. Gegenw.*, Berlin, 1907, xlviii. 207.
29. Lambert, *Trans. Assoc. Amer. Phys.*, Philad., 1907, xxii. 607.
30. Langdon Brown, *Clin. Journ.*, Lond., 1908, xxxi. 109.
31. Lenhartz, *Verhandl. d. Kongr. f. inn. Medicin*, Wiesbaden, 1909, 232.
32. Lenhartz, *Mitt. a. d. Hamburg. Staatsk.*, 1906, vi. 345.
33. von Leube, W., *Deutsch. med. Woch.*, 1909, xxxv. 961.
34. Martin, S., *Functional and Organic Diseases of the Stomach*, Edinb. and Lond., 1895.
35. Matthes, *Verhandl. d. 12. Cong. d. inn. Med.*, 1893, 425.
36. Mayerle, *Boas' Archiv f. Verdauungskr.*, Berlin, 1909, xv. 337.
37. Miller, C. H., *Archives Path. Instit. London Hospital*, 1906, i. 39.
38. Minkowski, *Med. Klinik*, 1905, i. 1333.
39. Moynihan, *Duodenal Ulcer*, Philad. and Lond., 1910.
40. Morison, Rutherford, and Drummond, *Brit. Med. Journ.*, 1909, ii. 67.
41. Paterson, Herbert J., *Gastric Surgery*, Lond., 1906.
42. Pavy, *Medical Times and Gazette*, 1863, ii. 285.
43. Pawlow, J. P., *The Work of the Digestive Glands*, Lond., 1902, 171.
44. Quenu, *Société de Chirurgie, Bulletins et Mémoires*, 1904, xxx. 447.
45. Quinke und Daettwyler, *Deutsch. med. Woch.*, 1882, viii. 79.
46. Robson, Mayo, *Brit. Med. Journ.*, 1906, ii. 1345.
47. Rolleston, H. D., *Brit. Med. Journ.*, 1903, ii. 1041.
48. Rolleston and Oliver, *Brit. Med. Journ.*, 1909, i. 1296.
49. Rolleston and Tebbs, *Brit. Med. Journ.*, 1904, ii. 114.
50. Rosenheim und Ehrmann, *Deutsch. med. Wochenschr.*, 1910, xxxvi. 111.
51. Schmidt, A., *Deutsch. med. Woch.*, 1906, xxxii. 1900.
52. Schmidt, A., *Verhandl. d. 20. Congr. f. inn. Med.*, 1902, 270.
53. Senator, *Therap. d. Gegenw.*, Berlin, 1907, xlviii. 250.
54. Senator, *Verh. f. inn. Med.*, 1906, Jan.
55. Spriggs, E. I., Oliver-Sharpey Lectures, *Lancet*, Lond., 1906, i. 1157.
56. Spriggs, E. I., *Brit. Med. Journ.*, 1910, i. 1216.
57. Spriggs, E. I., *Brit. Med. Journ.*, 1909, i. 825.
58. Spriggs, E. I., *Med.-Chir. Trans.*, Lond., 1907, xc. 283.
59. Spriggs, E. I., *Clin. Journ.*, Lond., 1907, xxx. 222.
60. Türk, *Journ. of Med. Research*, 1908, xvii. 355.
61. Wagner, *Münch. med. Wochenschr.*, 1904, li. 1.
62. Walko, K., *Centralbl. f. inn. Med.*, 1902, xxiii. 1113; *Wien. klin. Wochenschr.*, 1907, xx. 1457.
63. Weintraud, *Berl. klin. Wochenschr.*, 1909, xlvii. ii. 2281.
64. Westphalen, H., *St. Petersb. med. Wochenschr.*, 1909, xxxiv. 1.
65. White, W. Hale, *Lancet*, Lond., 1906, ii. 1189.
66. Willcox, W. H., *Quart. Journ. of Med.*, Oxford, 1909, iii. 93.
67. Wirsing, *Archiv f. Verdauungskr.*, Berlin, 1905, xi. 197.
68. Wolff, *Sammlung klin. Vorträge*, Leipzig, N. F., 'Innere Medizin,' Abt. 181, 182, 315.
69. van Yzeren, W., *Zeitschr. f. klin. Med.*, Berlin, 1901, xliii. 180.



# SOME POINTS IN RELATION TO THE AETIOLOGY OF AURICULAR FIBRILLATION

By C. E. LEA

With Plate 39

## I. *The Recognition of Auricular Fibrillation as a Specific Clinical Entity.*

WHEN the auricle is contracting in response to sinus stimulation, the wave of auricular contraction thereby produced passes over the auricle from the neighbourhood of its junction with the superior vena cava, towards the auriculo-ventricular junction. Such a wave constitutes the auricular systole. The auriculo-ventricular bundle conducts this impulse to the ventricle and the latter contracts in response, normally at an interval of 0.12 to 0.16 second after the auricular systole.

It has been shown that there is a definite condition of the auricle, namely, fibrillation of its musculature, in which this normal sequence of events is considerably modified. In this condition the regular wave of auricular contraction is absent, being replaced by irregular wavelets of contraction, said to be produced simultaneously by irregularly distributed foci of varying excitability throughout its musculature. Seen naked eye, in experimental conditions upon the dog, the auricular chamber is 'ballooned' and over the walls fine tremors are observed. In electro-cardiographic tracings such tremors are recorded as small waves, of varying size and frequency, occurring at the rate of 200 to 300 oscillations per minute.

The effect of this fibrillation upon the ventricle is dependent upon the conducting power of the auriculo-ventricular bundle. Clinically, when such a condition is recognized, ventricular systoles become markedly irregular, both as regards the force and frequency of their contractions, and it is assumed that such arrhythmia is due to the irregular impulses received by it from the disturbed auricle.

The character of the polygraphic tracing taken in such cases shows two distinctive features: first, continuous irregularity both in size and frequency

of the ventricular systoles, with absence of relationship between height of ventricular wave and the length of preceding diastolic interval, a feature which distinguishes it from extra-systoles, when such a relationship is present; and, secondly, absence of the auricular wave  $\alpha$ , and the presence of the ventricular form of venous pulse.

These distinctive characters, easily recognizable by graphic methods, enable one thus to establish auricular fibrillation as a definite clinical condition. Even for practical purposes, in the absence of complete electro-cardiographic tracings, in which the actual waves due to fibrillation can be readily demonstrated in a few favourable cases, such fibrillation waves can be seen in polygraphic tracings.

## II. *The Aetiology of Auricular Fibrillation.*

It was recognized that this form of arrhythmia was identical with that frequently present in mitral valvular disease, and it was in mitral stenosis, more especially, that this arrhythmia was chiefly studied. But the subjective and objective symptoms with which it was associated in this pathological condition were very variable. There may or may not be dyspnoea, and in many cases there seemed little relationship between the severity of the symptoms and the presence or absence of auricular fibrillation. Further, mitral stenosis is, in many instances, unaccompanied by fibrillation. Thus Dr. T. Lewis, in 72 unselected cases of mitral stenosis, found auricular fibrillation present in 20.8 per cent. (3), and in a series of 13 unselected cases of the present writer auricular fibrillation was present in 37.6 per cent. (2). Finally, there remains a considerable number of cases in which auricular fibrillation occurs in the absence of mitral valvular disease, or in cases presenting objectively no other signs of cardiac lesion, but associated with symptoms suggestive of limitation of the field of cardiac response. It becomes necessary, therefore, to consider auricular fibrillation as a definite condition, and to record with as much accuracy as possible the various conditions under which it occurs, with a view to ascertaining the probable etiological factors concerned in its production.

## III. *Method of Investigation.*

The scope of the present inquiry is limited to 69 cases of auricular fibrillation. Such cases were for the most part examined in the wards of the Union Infirmarys in and around London, and in some of the general hospitals, and I am much indebted to the medical superintendents and the honorary staff of these hospitals for the kindness with which they allowed me to make use

of the clinical material under their care. The examination of each case was made as complete as possible, and in nearly every case (91.5 per cent.) polygraphic records were obtained. In thirteen of the cases such records were supplemented by electro-cardiographic records; for the publication of some of these, and for other valuable assistance, I am indebted to Dr. Thomas Lewis, University College, London.

TABLE I.

1. Number of cases examined . . . . .	69
2.    "    "    "    with polygraphic record . . . . .	63
(a) Jugular and radial . . . . .	35
(b) Radial only . . . . .	17
(c) Jugular, radial and electro-cardiogram . . . . .	9
(d) Radial and electro-cardiogram . . . . .	4
3.    "    "    "    in which clinical examination and history alone obtained . . . . .	6

Though auricular fibrillation may be recognized as a definite clinical condition its exact pathology is as yet not so definitely understood. Sufficient evidence has not been accumulated to substantiate the view that it is due to fibrosis of the auricular musculature, and until such evidence, either in support of or against this view, is forthcoming, it is impossible to differentiate clearly between direct and indirect causes, between the cause of, and pathological conditions concomitant with, auricular fibrillation.

But a study of the lesions in which it is found renders it possible to see some association between auricular fibrillation and rheumatic fever or chorea, mitral stenosis, and probably arterio- or cardio-sclerosis, and in view of the prominence with which these pathological conditions are associated with it, the following subdivision of the facts here collected has been made (it is assumed that auricular fibrillation is due to some pre-existing pathological condition of some portion or portions of the body):—

(1) Cases of auricular fibrillation in which rheumatism or chorea has been present, with or without valvular disease.

(2) Cases of auricular fibrillation in which both are absent, with or without valvular disease.

*Auricular Fibrillation with preceding Rheumatic Fever or Chorea, or both.*

TABLE II.

Case No.	Sex.	Age.	Rheumatic fever attacks.		Chorea.	Cardiac lesion.	Other diseases.
			No.	Age.			
1	F.	26	1	26	—	Mitral stenosis	Scarlet fever
2	M.	41	2	20, 35	—	Mitral and aortic incomp.	Pneumonia, septic infection
3	F.	34	2	12, 30	—	Mitral stenosis and incomp.	—
4	F.	34	1	18	—	Mitral stenosis	—
5	F.	35	1	29	—	Mitral stenosis	—
8	F.	42	3	20, 38, 39	—	Cardiac dilatation	—
9	F.	50	1	16	14	Mitral stenosis	—
12	M.	28	3	15 ? 27	—	Mitral stenosis	—
13	M.	35	1	16	—	Arterio-sclerosis	Gonorrhoea, alcohol
15	M.	55	1	41	—	Cardiac dilatation	Scarlet fever
16	F.	35	2	7, 33	—	Mitral and aortic disease	—
18	M.	69	3	12, 33, 35	—	Arterio-sclerosis	Measles, scarlet fever, whooping-cough, influenza
19	M.	42	4	14, 28, 33, 37	—	Mitral stenosis	—
20	F.	32	3	13, 16, 20	—	Aortic and mitral disease	—
23	F.	60	2	14, 35	—	Arterio-sclerosis	Measles, whooping-cough
25	F.	45	2	33, 35	—	Mitral stenosis	—
28	M.	44	2	14, 28	—	Aortic and mitral disease	Influenza
29	F.	73	2	35, 38	—	Mitral stenosis	'Stroke', aged 61
31	F.	48	4	15, 25, 27, 31	—	Mitral stenosis	—
32	F.	37	—	—	16	Mitral stenosis	Measles
34	M.	43	1	14	—	Cardiac dilatation	Measles, empyema
35	M.	18	2	11, 16	—	Mitral stenosis	Measles, scarlet fever
37	M.	35	1	25	—	Cardiac dilatation	Measles, pneumonia, influenza
38	F.	49	2	8, 39	—	Arterio-sclerosis	Measles, whooping-cough
39	F.	49	2	10, 26	—	Cardiac dilatation	Occ. bronchitis
41	M.	41	1	17	—	Cardiac dilatation	Haemoptysis, hard work
43	M.	19	—	—	5	Mitral stenosis	Influenza frequently
44	F.	33	3	10, 13, 14	—	Mitral stenosis	Diphtheria, pneumonia, pericarditis
46	M.	36	1	16	—	Mitral stenosis	—
48	F.	17	1	16	10	Mitral and aortic disease	Measles, pneumonia, phthisis (?)
53	F.	50	1	15	—	Arterio-sclerosis	Measles, pertussis, scarlet fever, mumps, chicken-pox, influenza 3 times
55	F.	22	1	13	11	Cardiac dilatation	Occ. bronchitis
57	F.	40	1	?	—	Cardiac dilatation	Smallpox
61	M.	45	2	27, 45	—	Endocarditis	Measles, typhoid fever
64	F.	52	3	22, 29, 38	—	Mitral stenosis	Measles, scarlet fever, shingles, bronchitis, influenza
65	F.	26	1	14	—	Tachycardia, Graves' disease	Scarlet fever, chicken-pox, always delicate (and exophthalmos for 7 years)
67	M.	41	1 ?	37 ?	—	Cardiac dilatation	Measles, pertussis, scarlet fever, gonorrhoea and syphilis
69	M.	54	1	24	—	Arterio-sclerosis	Gout, alcohol, cirrhosis of liver
71	F.	40	1	18	8	Mitral stenosis	—

*Auricular Fibrillation without preceding Rheumatic Fever or Chorea.*

TABLE III.

<i>Case No.</i>	<i>Sex.</i>	<i>Age.</i>	<i>Cardiac lesion.</i>	<i>Preceding diseases.</i>
6	M.	49	Tachycardia	Graves' disease
7	M.	35	Arterio-sclerosis	Alcohol, hard work
10	F.	77	Aortic stenosis and incomp.	None
11	M.	44	Aortic stenosis and incomp.	—
14	M.	58	Arterio-sclerosis	Alcohol
17	M.	76	Arterio-sclerosis	Occasional bronchitis
21	F.	54	Cardiac dilatation	Measles, scarlet fever, pneumonia
22	F.	64	Arterio-sclerosis	Measles, diphtheria, bronchitis
24	M.	64	Arterio-sclerosis	Scarlet fever, influenza
26	M.	45	Cardiac dilatation	Measles, pertussis, mumps, shingles, influenza, rheumatoid arthritis
27	M.	55	Arterio-sclerosis	—
30	F.	70	Cardiac dilatation	Bronchitis, starvation and neglect
33	M.	51	Mitral stenosis	Measles, smallpox, influenza, alcohol
36	M.	29	Mitral stenosis	Influenza, pneumonia, aged 28
40	F.	74	Arterio-sclerosis	Measles, pertussis, mumps, 'fits,' aged 17 and 67
42	M.	61	Arterio-sclerosis	Measles, scarlet fever, malaria, rheumatoid arthritis, hemiplegia, aged 55, influenza aged 55
45	M.	67	Arterio-sclerosis	Scarlet fever, smallpox, gout, influenza
47	F.	35	Cardiac dilatation	Scarlet fever, pertussis, measles
49	M.	35	Arterio-sclerosis	Heavy tobacco-smoker, hard work
52	M.	70	Cardiac dilatation	Bronchitis
54	M.	70	Cardio-sclerosis	Syphilis, gonorrhoea, influenza
56	F.	53	Cardiac dilatation	Typhoid, pneumonia
58	F.	58	Arterio-sclerosis	Measles, chronic bronchitis, influenza
59	M.	51	Arterio-sclerosis	Gonorrhoea, bronchitis,
60	M.	55	Arterio-sclerosis	Renal calculus
62	F.	59	Arterio-sclerosis	Measles, occasional bronchitis
63	M.	46	Arterio-sclerosis	Influenza, aged 45
66	F.	46	Cardiac dilatation	Measles, scarlet fever, pertussis, mumps, influenza, aged 30
68	M.	38	Mitral stenosis	No illnesses
70	F.	35	Mitral stenosis	Anaemia as a girl, bronchitis, chicken-pox, influenza twice

IV. *The Relation of Auricular Fibrillation to Rheumatic and Choreic Conditions.*

An examination of the above tables, which include all the cases examined, records, briefly, the following facts:—(1) a rheumatic or choreic history precedes auricular fibrillation in 39 cases, i.e. 56.6 per cent. The family history of rheumatism was not sufficiently inquired into, in the series of cases, but according to some authorities such inquiry would have elicited an additional 10 per cent. of cases in which such history could be obtainable. The frequency of rheumatic fever in these cases: 4 attacks, 2 cases; 3 attacks, 6 cases; 2 attacks, 11 cases; single attack, 20 cases. (2) The absence of such history occurs in 43.4 per cent. (3) The average age incidence of auricular fibrillation cases in the two classes shows an earlier age incidence in the rheumatic cases, 40.3 years as



compared with 53.1 years in the non-rheumatic. (4) The rheumatic cases were more frequent in females than males, in the proportion of 23 to 16 respectively; in non-rheumatic cases males were more frequently the subject of auricular fibrillation, being 18 as compared to 11 females.

In the tables above it will be seen that every case is associated with a diagnosis of the supposed cardiac condition. In a few cases such diagnosis has been confirmed on subsequent pathological examination, but in the large majority such a consummation was not forthcoming. Before considering, therefore, the relationship of auricular fibrillation to the condition of the cardio-valvular system in these cases, it is essential that there should be a definite apprehension of the main points upon which such diagnoses have been made. A full and detailed inquiry into the clinical signs in each case cannot, for obvious reasons, be entered into here, but the main lines upon which the diagnosis is tentatively offered here may be stated briefly.

No case has been diagnosed as mitral stenosis in the absence of a diastolic murmur, heard with greatest distinctness in the region of the apex. Such murmur may be of variable duration, intensity, or time relationship to the diastolic interval, and may or may not be associated with an altered first sound or systolic murmur. In most of the cases noted there was, on percussion, a variable increase of extension of the cardiac dullness to the right of the sternum.

The diagnosis of cardiac dilatation embraces not only cases of myocardial degeneration, but probably includes, more especially in those cases with preceding rheumatic history, varying degrees of mitral incompetency, associated with stenosed or altered character of the mitral valve area. The clinical signs upon which most stress has been laid in these cases have been the presence of a well-defined systolic murmur of maximum intensity in the apical region, and increased cardiac dullness, both to the left and to the right. The history of the cases suggests also, in many instances, the possible cause of the dilatation.

The diagnosis of arterio-sclerosis embraces a considerable number of cases. The condition of the arteries has in many cases suggested, more than have the physical signs to be made out in the heart, the nature of the lesion. In all such cases, however, there have been symptoms of limitation of the field of cardiac response. The patients included under this diagnosis have been of a greater average age than those in the valvular cases.

It is suggested that for a broad basis upon which to consider the heart condition with which auricular fibrillation is associated, the above details, associated with a full consideration of the varying factors present in each individual case, may be taken as sufficiently accurate.

Recognizing the predominant influence of rheumatic and choreic infections in relation to subsequent valvular and myocardial lesions, the cases in which such diseases have been present have been separated from those in which they have been absent. In the latter class, however, inquiry into preceding and possible etiological factors in the form of illness or mode of life has been instituted, and a classification of them has been made, with a view to noting any

possible etiological relationship. The result of such inquiry, together with the character of the cardiac lesions in the two classes of cases, is tabulated in the following table.

TABLE IV.

	<i>Preceding rheumatic or other disease.</i>	<i>Mitral stenosis.</i>	<i>Aortic and mitral regurgi- tation.</i>	<i>Cardiac dilat- ation.</i>	<i>Arterio- or cardio- sclerosis.</i>	<i>Other conditions.</i>
A. Rheumatic fever	13	4	8	7	Rheumatic endocarditis	1
Rheumatic fever and chorea	2	1	1	—	Graves' disease	1
Chorea	2	—	—	—		
B. Non-rheumatic	4	—	7	16	Graves' disease	1
Preceding Illnesses in Class B <sup>1</sup>						
1. Measles	1	—	4	5		
2. Scarlet fever	—	—	3	3		
3. Pertussis	—	—	3	1		
4. Diphtheria, mumps, chicken-pox, ty- phoid	1	—	4	2		
5. Gout, shingles, malaria, cirrhosis	—	—	1	1		
6. Smallpox	1	—	—	1		
7. Pneumonia	1	—	2	—		
8. Bronchitis	1	—	2	4		
9. Influenza	3	—	2	6		
10. Gonorrhoea, syphilis	—	—	—	2		
11. Alcohol or hard work	—	—	—	2		

<sup>1</sup> In these cases there is 'overlapping', since single cases may have had one or more of the above diseases.

#### V. *The Relation of Auricular Fibrillation to the associated Cardiac Lesion.*

The following is the order of relative frequency of incidence of fibrillation in cardiac conditions, the percentages referring to the percentage of total number of cases of auricular fibrillation observed: Arterio- or cardio-sclerosis, 32.8 per cent.; mitral stenosis, 31.3 per cent.; cardiac dilatation, 23.8 per cent.; mitral and aortic incompetence, 7.1 per cent.; other conditions, rheumatic endocarditis (1 case), Graves' disease (2 cases), 4.4 per cent.

Two points must be referred to in consideration of these figures: first, the cases of cardiac dilatation are likely to include in their number a few in which mitral stenosis was also present, or at any rate primary mitral valvular disease. Therefore the percentage 31.3 per cent. given for mitral stenosis must be accepted as the lowest estimate, and it is probably a higher figure. And, secondly, the almost equal incidence of mitral disease and arterio- or cardio-sclerosis. The remarks applied to cardiac dilatation and its association with primary mitral valvular disease may in some degree, but to a less extent, apply also to cardio-sclerosis.



arterio-sclerotic cases. Care was taken in inquiring into this illness, and no case accepted which did not show definite history of feverishness and pains in limbs, compelling the patient to be in bed for variable periods.

*Electro-cardiographic evidence.* Electro-cardiographic tracings were taken of 13 unselected cases in the series by Dr. T. Lewis, University College, London, using the string galvanometer of Einthoven (Edelmann's modification). There were 4 female and 9 male cases. In all cases the curves characteristic of auricular fibrillation were obtained. For a detailed description of such curves and their interpretation, the reader is referred to Dr. Thomas Lewis's (3) paper in *Heart*, Vol. i. A typical tracing is put on record here (Case 36), together with a polygraphic record obtained by Mackenzie's ink polygraph at the same time (Plate 39). In the subjoined table are recorded briefly the main clinical and graphic features in the cases which were examined electro-cardiographically.

TABLE V.

<i>Case No.</i>	<i>Sex.</i>	<i>Age.</i>	<i>Diagnosis.</i>	<i>Physical signs.</i>	<i>Ventricular type, venous pulse.</i>	<i>Electro-cardiogram.</i>
21	F.	54	Cardiac dilatation	Orthopnoea, venous pulsation in neck. 3rd rib Ht. $\frac{2''}{2''}   1''$ left of NL. Systolic murmur tricuspid area, 1st and 2nd sound, sharp and clear elsewhere	Present	Prominent oscillations, T. variation inverted
33	M.	51	Mitral stenosis	Ht. dullness 3rd rib $\frac{2''}{2''}   \text{NL.}$ Sounds dull, fairly loud 1st sound, double 2nd all areas. At apex and tricuspid areas succeeded by diminuendo diastolic, not sustained throughout diastolic pause	Present	Prominent oscillations, maximal over auricle. No intrinsic ventricular beats
36	M.	29	Mitral stenosis	Dyspnoeic on exertion. Apex local forcible under 5th rib 1" R. NL. Ht. dullness 3rd rib $\frac{2''}{2''}   \text{NL.}$ Soft systolic replaces 1st sound at apex, followed by long diastolic occluding 2nd sound. Systolic, harsh in character at aortic, not conducted down sternum	Present	Very prominent oscillations, maximal over auricle (see Figs. 1-4)
44	F.	33	Mitral stenosis	Very dyspnoeic. Ht. 3rd rib dullness $\frac{2''}{2''}   6\frac{1}{4}''$	Present	Oscillation poor with right arm and left leg; oscillations obtainable by special lead over chest wall, maximal near auricle

TABLE V (continued).

<i>Case No.</i>	<i>Sex.</i>	<i>Age.</i>	<i>Diagnosis.</i>	<i>Physical signs.</i>	<i>Ventricular type, venous pulse.</i>	<i>Electro-cardiogram.</i>
48	F.	17	Mitral stenosis	Dyspnoea. Apex beat 6th space. Ht. dullness 3rd rib $\frac{1\frac{1}{2}''}{16\frac{1}{2}''}$ . Systolic murmur at apex. Diastolic murmur aortic area	Present	Poor oscillations (just present); intrinsic ventricular beats (bigeminal)
54	M.	43	Cardiac dilatation	Marked venous pulsation in neck. Some thickening of arteries. Ht. dullness 3rd rib $\frac{2\frac{1}{2}''}{NL}$ . Impure 1st sound at apex. Elsewhere normal	Present	Prominent oscillations; no intrinsic ventricular beats
51	M.	60	Cardio-sclerosis	Looks well. Ht. dullness 3rd rib $\frac{2''}{4\frac{1}{2}''}$ . Arterio-sclerosis. Ht. sounds normal	Present	Oscillations present; occasional intrinsic ventricular beat
57	F.	40	Cardiac dilatation	Much dyspnoea on exertion. Some venous pulsation in neck. Pulse rapid, irregular. Ht. dullness 3rd rib $\frac{2\frac{1}{2}''}{17\frac{1}{2}''}$ . Soft systolic murmur with 1st sound at apex. 2nd sound normal, systolic heard at tricuspid but less loud	Radial only. Venous pulse not obtainable	Well-marked oscillations; no intrinsic ventricular beats
58	F.	58	Arterio-sclerosis	Looks well, arteries slightly thickened. Ht. dullness 3rd rib $\frac{2''}{5''}$ . Ht. sound normal	Radial only. Venous pulse not obtainable	Oscillations maximal over auricle; numerous intrinsic ventricular beats
60	M.	55	Cardio-sclerosis	Dyspnoea on exertion. Ht. dullness 3rd rib $\frac{1\frac{1}{2}''}{4\frac{1}{2}''}$ . Sounds very feeble and distant; impure 1st sound at apex	Present	Oscillations well marked from time to time; maximal over right auricle; type of curve given by lesion of right branch of auriculo-ventricular bundle. Cf. Fig. 6
67	M.	41	Arterio-sclerosis	Few subjective symptoms. Ht. dullness 3rd rib $\frac{2''}{4\frac{1}{2}''}$ . Soft systolic murmur replacing 1st sound at all areas. 2nd sound variable in intensity	Present	Oscillations prominent over auricle; no intrinsic ventricular beats

TABLE V (*continued*).

<i>Case No.</i>	<i>Sex.</i>	<i>Age.</i>	<i>Diagnosis.</i>	<i>Physical signs.</i>	<i>Ventricular type, venous pulse.</i>	<i>Electro-cardiogram.</i>
68	M.	38	Mitral stenosis	Has few subjective symptoms. Ht. dullness 3rd rib $\frac{1''}{1'' NL.}$ . 1st sound clear and loud, associated with systolic murmur of even intensity, double 2nd; faint diastolic, diminuendo in character, heard at apex	Present	Oscillationsmaximal over auricle; no intrinsic ventricular beats
69	M.	54	Cardio-sclerosis	Ht.dullness $\frac{3rd\ rib}{1'' NL.}$ . Sharp, short. 1st sound at apex and systolic murmur; double 2nd pulmonary area. Sounds rather feeble	Present	Oscillationsmaximal over auricle; no intrinsic ventricular beats

*Chief Conclusions.*

1. Auricular fibrillation as a definite clinical entity can be recognized.
2. Rheumatic or choreic disease preceded auricular fibrillation in 56.6 per cent., the most frequent lesion to which it gave rise being mitral stenosis (43.6 per cent. of cases with rheumatic history).
3. Non-rheumatic cases present auricular fibrillation in 43.4 per cent., the most frequent cardiac lesion being cardio- or arterio-sclerosis, 57.1 per cent.
4. The age incidence of mitral valve disease, with or without preceding rheumatism, was 38.2 years; the age incidence of cardio-sclerosis was 53.9 years in rheumatic cases, 56.9 years in non-rheumatic.
5. Females were more frequently subject to valvular disease than male in the proportion of 16 to 10; males were more subject to arterio- or cardio-sclerosis, 15 to 8.
6. Of all cases of auricular fibrillation, 32.8 per cent. occurred in cardio-sclerosis, 31.3 per cent. in mitral stenosis, and 23.8 per cent. in cardiac dilatation.
7. Influenza was noted as having occurred in 39.3 per cent. of non-rheumatic cases.
8. Electro-cardiographic records confirm, in all cases examined, the polygraphic records.

## REFERENCES.

1. Eppinger, H., and Stöck, C., 'Zur Klinik des Electrocardiograms,' *Zeitsch. f. klin. Med.*, 1910, lxxi. 157-64.
2. Lea, C. E., *Medical Chronicle*, 1909.
3. Lewis, T., *Heart*, i. 306-72.

## DESCRIPTION OF FIGURES.

In the accompanying Plate 39 are inserted three curves, 1-3, representing the features usually seen in auricular fibrillation. Compare with normal curve, Fig. 4.

FIG. 1 (Case 36). Prominent oscillations, *ff*, due to fibrillation, replacing the normal auricular systolic wave *P* (Fig. 4); ventricular beats *R, S, T* are irregularly placed. Electrodes placed over 3rd and 5th ribs, right side, at their junction with sternum. The electrode site first mentioned is connected to the bottom of the string, as is the right arm and right arm-left leg leads.

FIG. 2 (same case). Electrodes placed at junction of 2nd rib, right side, with sternum and 4th right rib with sternum. Same oscillations, *ff*, absence of auricular wave *P*, and ventricular beats *R, S, T*, irregularly placed.

FIG. 3 (same case), showing the absence of oscillation in leads from the 3rd space, left anterior axillary line, and apex, i. e. over site of ventricles. Ventricular beats *R, S, T* very prominent.

FIG. 4 (same case) is a polygraphic tracing taken by Mackenzie's ink polygraph at same time as the above tracings, showing (i) complete irregularity of ventricular beats; (ii) absence of auricular wave, *a*; and small irregular wavelets between the ventricular beats, probably due to auricular fibrillation waves conducted to the jugular bulb.

FIG. 5 is an electro-cardiogram taken with leads from right arm and left leg. This is a normal electro-cardiogram. Note the waves *P* due to auricular systole, *R, S, T* due to ventricular systole.

FIG. 6 (Case 60). An electro-cardiogram taken with leads from right arm and left leg. There is no trace of the normal *P* wave; it is replaced by oscillations *ff*. The ventricular complex has the outline recognized as the result of section of the right branch of the *a-v* bundle.

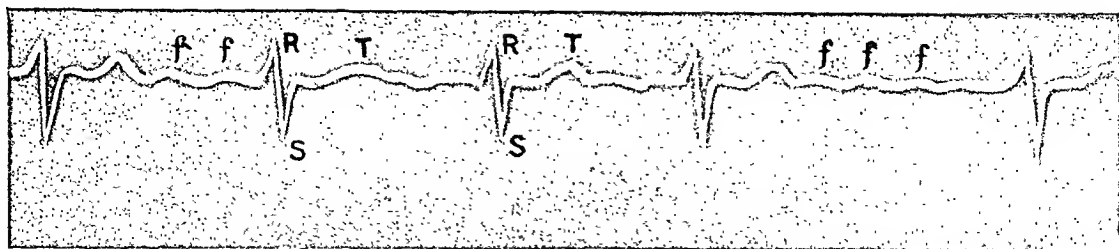


FIG. 1

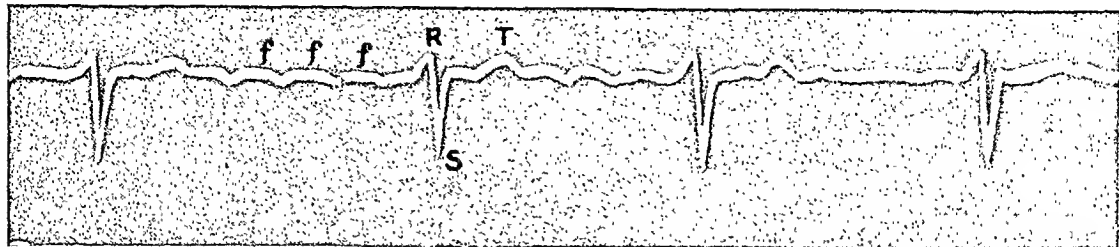


FIG. 2

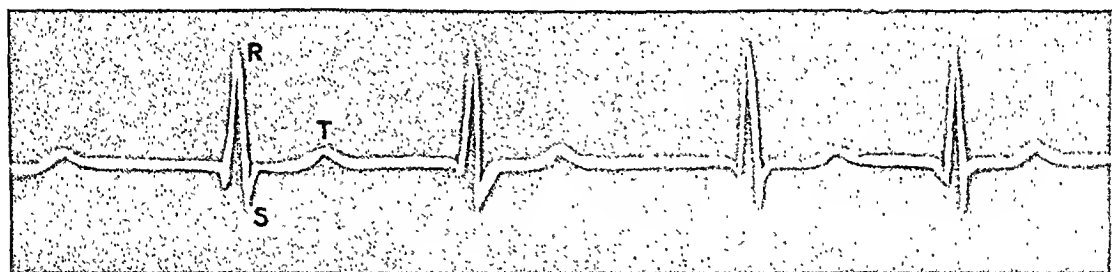


FIG. 3

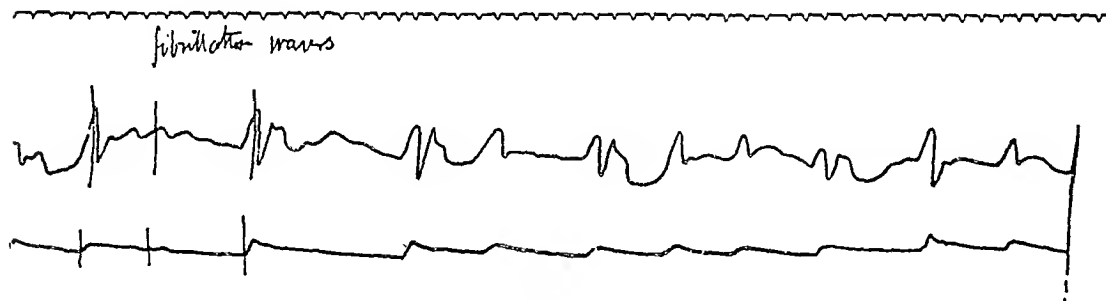


FIG. 4

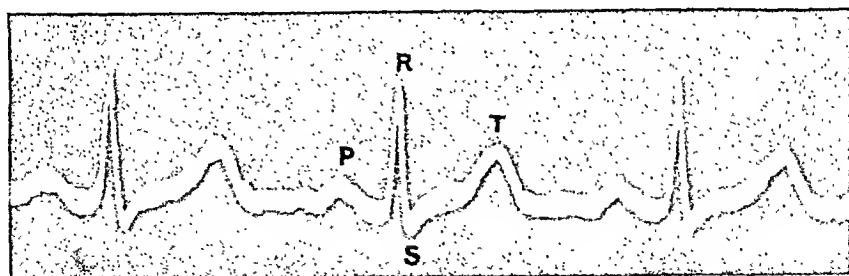


FIG. 5

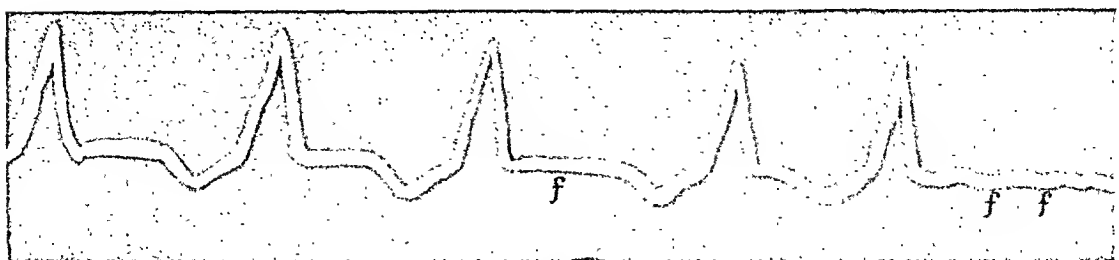


FIG. 6





# OBSERVATIONS ON THE RELATIONSHIP OF THE HEART-BEAT TO PULSUS ALTERNANS

By J. DAVENPORT WINDLE

With Plate 40

THE name *pulsus alternans* is properly given only to that form of pulse in which a strong beat is regularly followed by a weaker one, the duration of the pulse periods is generally equal although at times there may be slight alternation in the rhythm of the beats as well as in their force; but the difference in duration from one pulse to the next is always small, and invariably the longer period belongs to the stronger; in other words the occurrence of the weaker beat is slightly delayed.

*Pulsus alternans* has thus well-defined specific characters and its recognition is important in clinical work, since it is the expression of an exhausted heart and has prognostic significance. The term is, however, often erroneously applied to any kind of pulse when the beats alternate in force, irrespective of their rhythm; thus when an extra-systole regularly succeeds each normal beat the resemblance to *pulsus alternans* is close, since the beats alternate in strength, but the weaker beat occurs prematurely and is followed by a longer pause than that succeeding the stronger beat, whereas in true alternation the shorter pause succeeds the weaker beat.

*Pulsus alternans* has always been ascribed to alternate variation in strength of the ventricular contractions and the stronger beat of the heart synchronizing with the more forcible of the pulse, and the contrary was unquestioned until Hering (1), in 1894, directed attention to the fact that the simultaneous cardiogram and arterial pulse wave did not always coincide in height. He observed that at times the larger curve of the heart-beat was opposed to the smaller pulse, and vice versa. The observations were made on a clinical case, subsequently reported in detail by Rühl (3). Amongst the curves from cases of *pulsus alternans* published by Volhard (4) there are two which show the same phenomenon, but no systematic investigations on the subject appear to have been carried out on clinical cases, and there are but few published records illustrating the pulse and heart-beat in *pulsus alternans*. I made observations extending over a year on twelve patients with *pulsus alternans* coming under my care, with a view to determining the relation of the strength of the heart-beat to that of the radial pulse. To this end attention was paid to the character

of the sounds and impulse of the heart, and simultaneous polygraphic records of the cardiac and radial and jugular and radial pulsations respectively were taken in all cases possible. A paper by Hering (2) bearing on this question having recently come under my notice prompts me to set out briefly some of the facts observed.

*The Relationship of the Apex Beat of the Left Ventricle  
to Pulsus Alternans.*

My tracings show that it is exceptional to find definite alternation in the cardiogram taken from the apex beat of the left ventricle. There was some evidence of this in the record from one case only, reproduced in Fig. 1. This patient suffered from angina pectoris; the tracing was taken during a severe paroxysm. The degree of alternation is slight but decided. The relationship of the curves shows the anomaly of the larger beat of the radial pulse coinciding

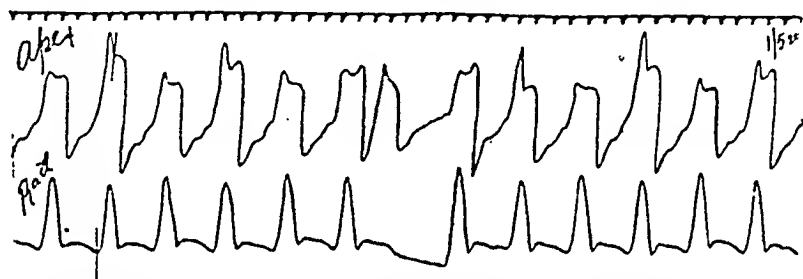


FIG. 1. Taken during a paroxysm of angina pectoris. The cardiogram is from the apex of the left ventricle: the smaller beat of the radial pulse coincides with the larger of the cardiogram.

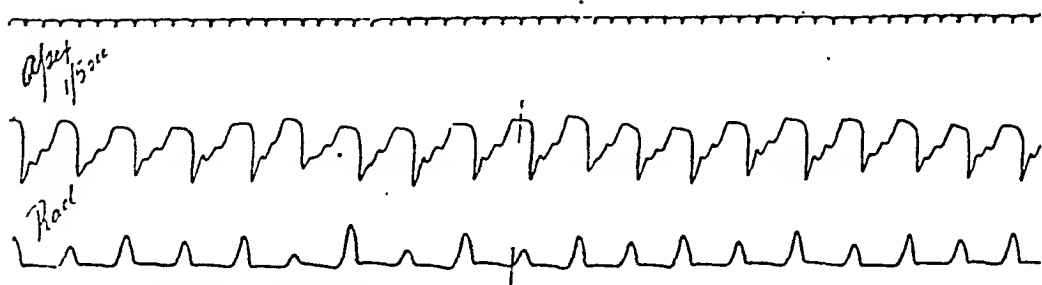


FIG. 2. From a patient with continuous *pulsus alternans*. The cardiogram was taken from the apex beat.

with the smaller of the heart-beat, a relation which is maintained throughout. No definite alternation in the heart-beat curves was present in records taken from the clinical apex beat in any of the other cases observed; on the contrary, in most patients the force of the left ventricle, as evidenced by the heart-beat curve, continued equal in strength while the radial pulse was markedly alternating. Thus Figs. 2 and 3 were obtained from a patient with an alternating pulse readily perceptible to the finger.

At times the alternation in force was so extreme that the pulse wave failed to reach the wrist; it would be expected under these circumstances that the cardiogram of the left ventricle would show a similar variation in force. In the figures the heart-beat curve is that of the left ventricle taken from the clinical apex beat. The apparently constant strength of the successive heart-

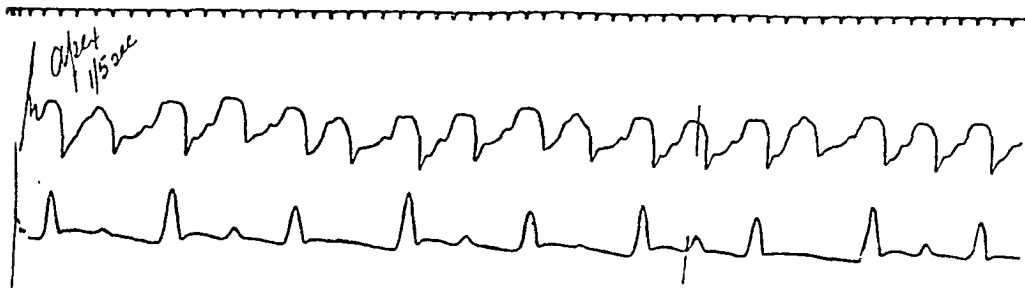


FIG. 3. From the same case as Fig. 2. taken at the same time. Shows higher degree of alternation in the radial pulse than the previous figure.

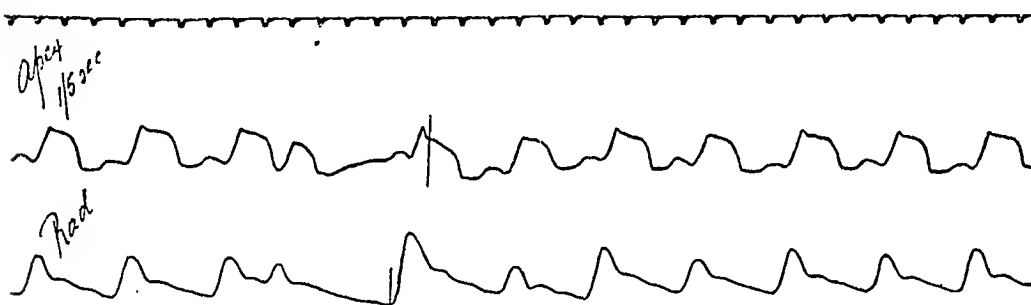


FIG. 4. Shows decided alternation in the radial tracing; the cardiogram is that of the left ventricle, taken from the apex beat. There is no disparity in force of the ventricular beats.

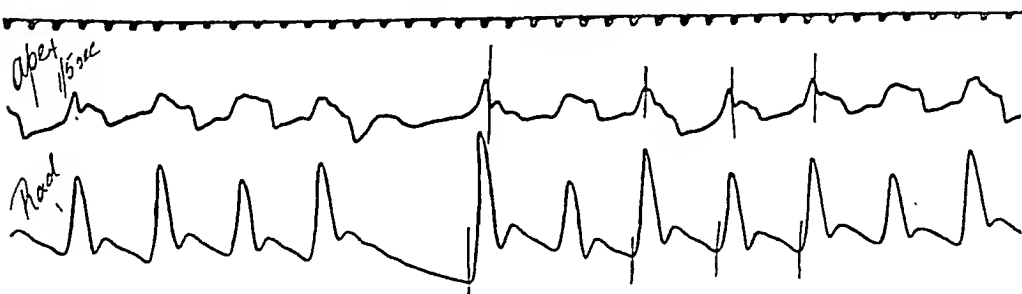


FIG. 5. From another case. Shows the same features as Fig. 4.

beats is in marked contrast to the extreme variations in height of the radial pulse; measurement of the pulse periods will show that the half frequency in Fig. 3 is due to true alternation, and not to extra-systoles, as may at first sight appear. The same discrepancy is shown in Fig. 4 from another case; there is decided alternation throughout the radial tracing, more marked immediately after the extra-systole. The cardiogram is that of the left

ventricle taken from the apex beat; it shows no disparity in force, or in the character of its curve, except in the extra-systoles and post-extra-systolic beats. The record shown in Fig. 5 was taken from another patient with continuous *pulsus alternans* and again illustrates the absence of correlation in force of the apex beat and radial pulse. The 'peaked' shape of the cardiogram which is shown bears no constant relation to the height of the radial waves; it coincides indifferently with the stronger and weaker radial beats.

It is noteworthy that a cardiogram of this shape occurs with the post-

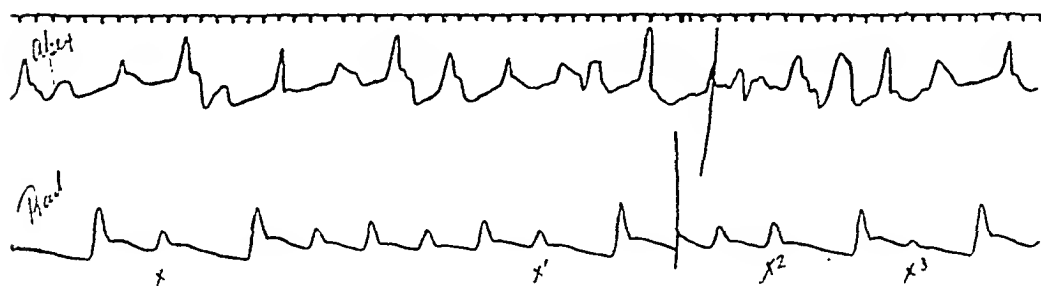


FIG. 6. Shows alternation and extra-systoles. The alternating radial beats at  $x$ ,  $x'$ , and  $x''$ , are followed by extra-systoles which fail to reach the wrist.  $x'''$  is a late extra-systole. There is no alternation in the cardiogram corresponding to that in the radial.

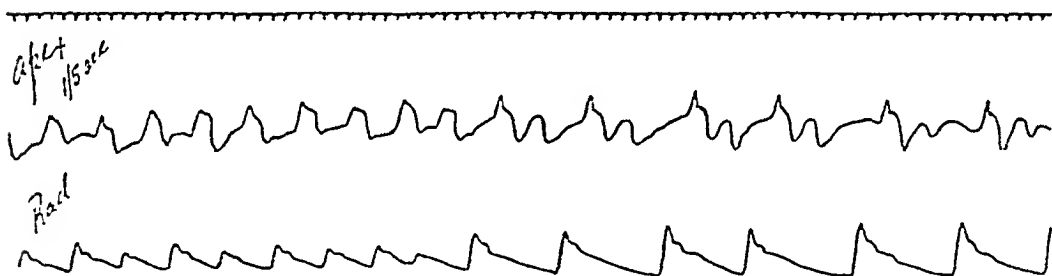


FIG. 7. Shows decided alternation in the radial pulses in the first part of the tracing without corresponding variations in the cardiogram. The apparent alternation in the heart-beat curve from the middle to the end of the tracing is due to an extra-systole after each normal beat, which fails to reach the wrist.

extra-systolic beats and also with the higher alternating beats in some of the tracings shown (Figs. 6, 7 and 16), but not with extra-systoles or the weaker alternating beats. In Fig. 6 there is a mixture of extra-systoles and alternation; the alternating radial beats at  $x$ ,  $x'$  and  $x''$  are followed by extra-systoles which fail to reach the wrist;  $x'''$  is a late extra-systole. There is clearly no alternation in the cardiogram corresponding to that in the radial. Fig. 7 again shows decided alternation in the radial pulses in the first part of the tracing without corresponding variations in the cardiogram; the half frequency of the radial pulse from the middle to the end of the tracing is due, as the eardiogram shows, to an extra-systole succeeding each normal beat which fails to reach the wrist, and not to true alternate heart action, since the longer pause belongs to the weaker beat. Fig. 8 was obtained from a case of continuous *pulsus alternans*

in which long runs of the rhythm shown were present when this curve was taken; there are three heart-beats to two of the radial pulse; the third beat in the cardiogram from the beginning of the tracing is an extra-systole not shown in the radial; this is followed by a large and small alternating beat, succeeded by an extra-systole, and so on. Apparently there is coincident alternation in force; but it may be questioned what features of the cardiogram are a measure of the strength of the ventricle.

The reason for the discrepancies evident in many of these tracings is not clear. In Fig. 1, for instance, we are confronted with the paradox of the stronger beat of the left ventricle coinciding with the weaker of the pulse, and vice versa. Again, in Figs. 2 and 3 the contraction of the ventricle is apparently forcible, and beat by beat keeps equal in strength, while the corresponding pulse exhibits at times extreme disparity in height. These anomalies are inexplicable except on the assumption that the strength of the apex beat is not a measure of the force exerted by the ventricle on its contents; in other words, that the contraction of the musculature which drives the blood out of the left ventricle is not represented in the apex curves. The suggestion, therefore, is that records from different areas of the heart may show alternation in one part and not in another.

Before illustrating observations on this point, the chief results of Hering's (2) recent experiments are shortly summarized. He found in dogs presenting *pulsus alternans* induced by glyoxalates that records taken from different areas of the praecordium with the chest wall intact differed as regards the relationships in force of the simultaneous cardiogram and arterial pulse. The animals were curarized, the vagi cut, and the curves taken during artificial respiration. The cardiograms were taken by air transmission: in one experiment (A) the heart-beat was registered from the fifth intercostal space; the arterial pulse with a Hürthle manometer in the carotid. The record very clearly shows the larger curve of the heart-beat corresponding to the smaller of the arterial pulse, and vice versa. On taking the record from the third left intercostal space—otherwise altering nothing in the experiment—the larger wave of the cardiogram was now found to coincide with the larger of the pulse, and vice versa. These results were constant, and repeatedly confirmed. After death of the animals needles were inserted through the intercostal spaces, at points from which the records were taken. On opening the thorax, the needle in the fifth space was found lodged in the left heart just above the apex. The needle in the third space was found in the neighbourhood of the conus of the right ventricle; from these facts the conclusion is reached that the cardiograms from the neighbourhood of the conus of the right ventricle and that from the region of the apex of the left ventricle are opposed. It is pointed out that these results were entirely in agreement with the records obtained in many experiments when tracings were taken directly from the myocardium by the suspension method.

In another experiment (B) under similar conditions, cardiograms from the fourth and fifth intercostal spaces were taken simultaneously with the carotid

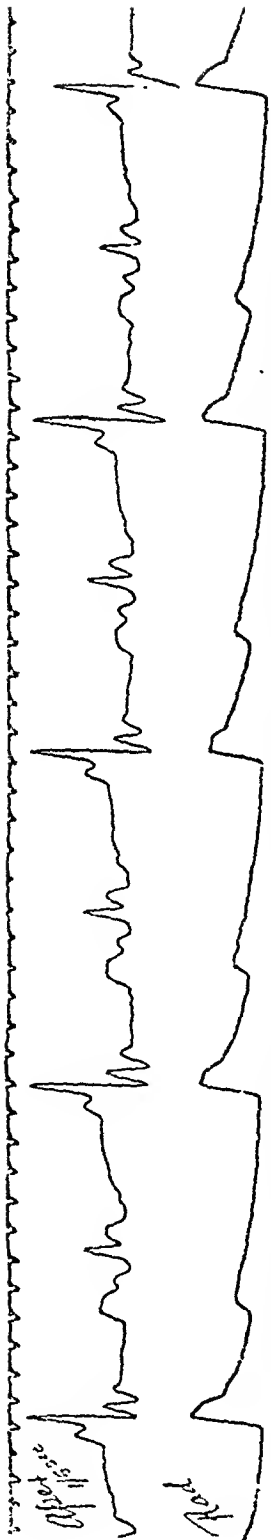


FIG. 8. Shows 3 heart-beats to 2 of the radial pulse. The third beat in the cardiogram from the beginning of the tracing is an extra-systole; this is followed by a large and small alternating beat, succeeded by an extra systole, and so on.

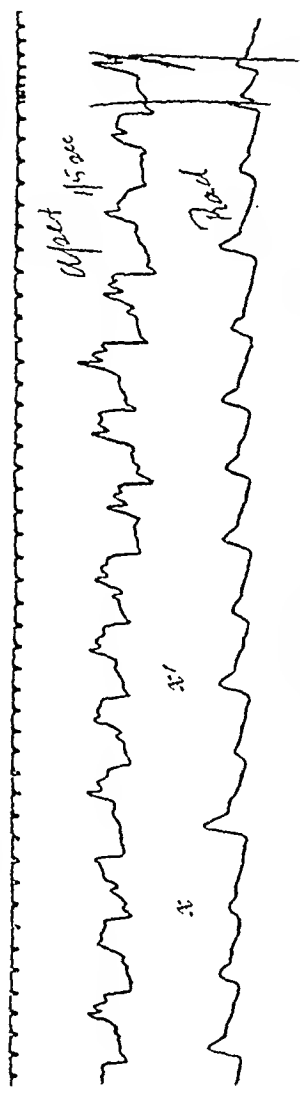


FIG. 9. Taken from the fifth space just outside the nipple line. The cardiogram is that of the left ventricle, in which there is no alternation. The radial pulse is markedly alternating.

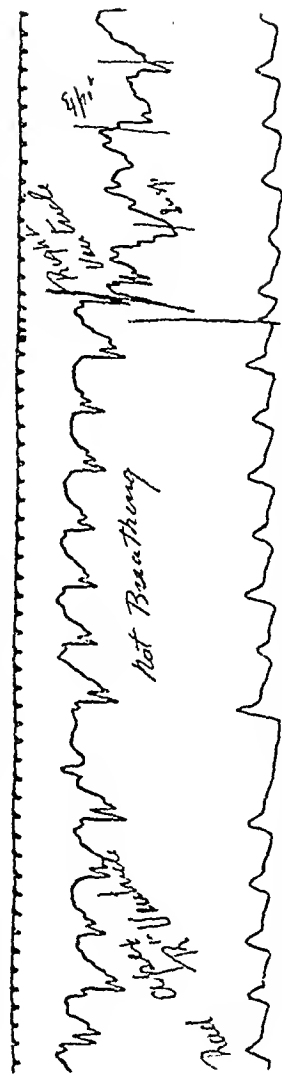


FIG. 10. From the same case as Fig. 9. The cardiogram is that of the right ventricle, and shows no disparity in force corresponding to the alternating radial beats.

pulse; the height of the three curves was in agreement until after the occurrence of a ventricular extra-systole, when the subsequent beats of the cardiograms were found to be opposed in height; the smaller of the fourth space and carotid pulse coinciding with the larger beat taken from the fifth space. In this instance also the insertion of needles in the fourth space entered in the neighbourhood of the conus of the right ventricle, and in the fifth space in the neighbourhood of the left ventricle.

The explanation advanced of these phenomena is in effect that alternately only a part of the musculature of the ventricle contracts. In proof of this Hering states that he observed, by direct inspection of the heart, that a partial contraction of the ventricle occurred with the smaller heart-beat recorded by the suspension method.

The view is expressed that records from similar areas of the praecordium taken from clinical cases will be found to present similar anomalies.

*The Relation of the Heart-beat Curve from Different Areas  
to the Radial Pulse.*

In the instances given there was no pulsation from which tracings were possible, other than at the situation of the clinical apex beat. In two of my patients, however, areas of pulsation were present in distinct parts of the praecordium from which tracings were taken. In the case from which Figs. 9 and 10 were obtained pulsation was present in the fifth space just outside the nipple line, and also in the sixth space close to the sternum. In Fig. 9 the radial beats at  $x$  and  $x^1$  occur a little prematurely; the rest of the beats are of true alternating character. The cardiogram is that of the left ventricle, in which there is manifestly no alternation. Fig. 10 was taken from the area close to the sternum; the heart-beat curve has the character of that of the right ventricle, and shows no disparity in force corresponding to the alternating radial beats.

In the other patient pulsation was present in the fourth left intercostal space for a distance of about 2 inches from the edge of the sternum; and also in the fifth left intercostal space 5 inches from the middle line at the site of the clinical apex beat. Tracings from these areas presented curious anomalies in the relationship of the height of the cardiogram and radial curve.

*Tracings of the fourth intercostal space.* Figs. 11-18 were obtained from the fourth left intercostal space, about  $1\frac{1}{2}$  inches from the edge of the sternum; it is difficult to say from which part of the heart the impulse arose; from its position it was probably the right ventricle; the cardiogram, however, has not the inverted character usually present in a right-ventricle impulse.

The figures are parts of a long continuous tracing. Fig. 11 shows decided and continuous alternation in the radial and cardiac curves; it exhibits the anomaly present in Fig. 1, the lower wave of the radial pulse coinciding with the higher of the cardiogram. In Fig. 12 there is no appreciable difference in the height of the individual beats of either curve. No explanation is apparent for



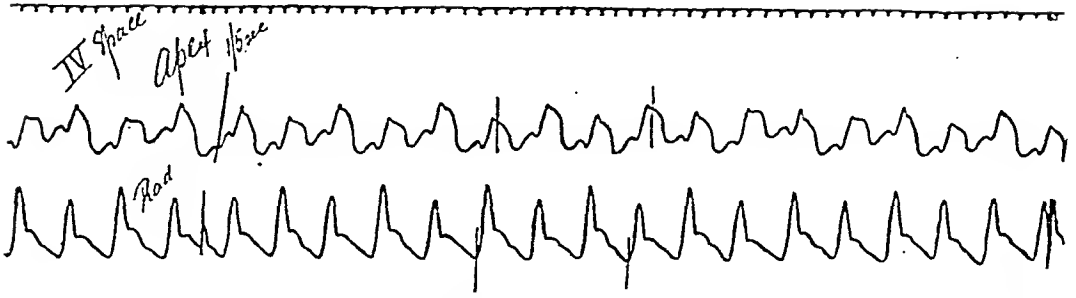


FIG. 11. The height of the radial curve and that of the cardiogram are opposed, the weaker beat of the radial pulse coinciding with the stronger of the heart. This and the following figures up to No. 18 were taken from the fourth left intercostal space, about  $1\frac{1}{2}$  inches from the edge of the sternum. The cardiogram in all these figures has the character of left-ventricle pulsation.

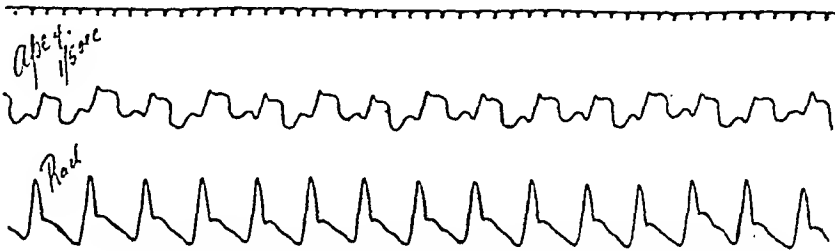


FIG. 12. Shows no appreciable alternation in either curve.

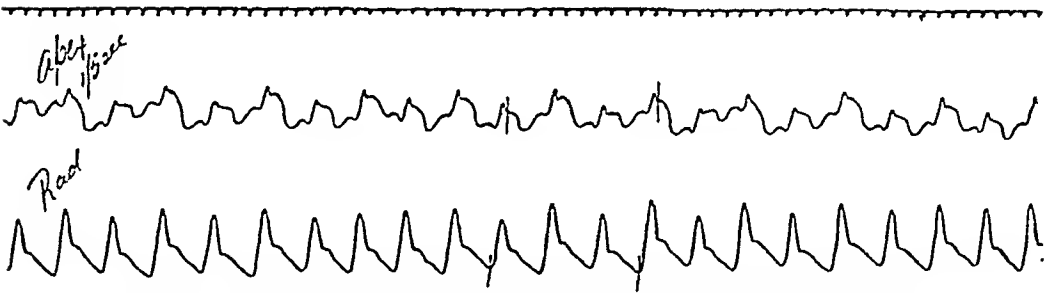


FIG. 13. High and low waves of the radial pulse and cardiogram coincide, the reverse relationship to Fig. 11.



FIG. 14. Shows alternation throughout in the cardiogram, while the radial pulse-beats in the first part of the tracing are equal. When alternation in the pulse begins the beats at first correspond in height with the cardiogram. After a few beats a reversed relationship is shown.

this change in the heart's action. I have directed attention (5) to the fact that the degree of alternation in continuous *pulsus alternans* may be increased or decreased, and at times disparity in force may be abolished apart from changes in the rate of the pulse sufficient to account for it; the suggested cause being attributed to respiratory variations in thoracic pressure.

On the recurrence of alternation shown in Fig. 13 a notable feature is the coincidence of the high and low waves of the radial pulse and cardiogram, the reversed relationship to that shown in Fig. 11.

In the next figure (Fig. 14) the cardiogram shows disparity in height throughout, while in the first part of the tracing the radial pulse-beats are equal; when alternation begins the big beat of the pulse corresponds with that of the

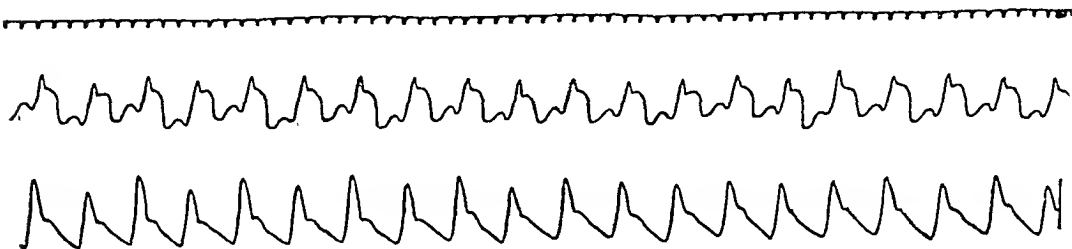


FIG. 15. Alternation is present in the first half of the radial pulse curve; the succeeding beats are approximately equal in height. The pulse rate is constant; there is no appreciable alternation in the cardiogram.

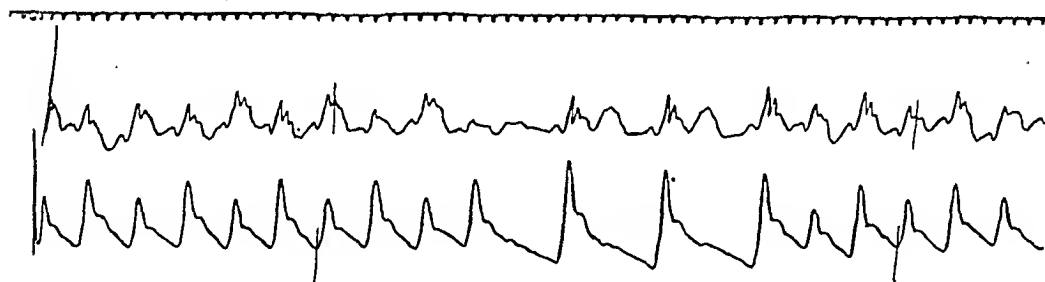


FIG. 16. The relationship in the height of the waves in the corresponding curves is reversed after the extra-systoles in the middle of the tracing.

heart for the first few beats; then a changed relationship ensues; the weaker pulse wave synchronizes with the stronger of the heart.

Still another anomaly is evident in the first part of Fig. 15, in that the beats of the cardiogram do not appreciably vary in force, whilst those of the radial pulse alternate. In the continuation of this tracing alternation occurred in both curves, the stronger beats coinciding.

Figs. 16, 17, and 18 are reproduced to show the relationship of the waves after extra-systole. In Fig. 16 the relationship of the waves becomes reversed after the group of extra-systoles shown in the middle of the tracing. In Fig. 17, with the increased degree of alternation succeeding the intermission at  $\infty$ , the anomalous relationship of high and low beats recurs. A curious feature in this

tracing is the absence of a premature beat in the cardiogram or radial curve during what is apparently an extra-systolic period, judging from the height of the succeeding wave. It may be that the intermission represents a complete systolic deficiency of the left ventricle; the compensatory pause is not complete, whereas in Fig. 16 each intermission is equal to three pulse beats.

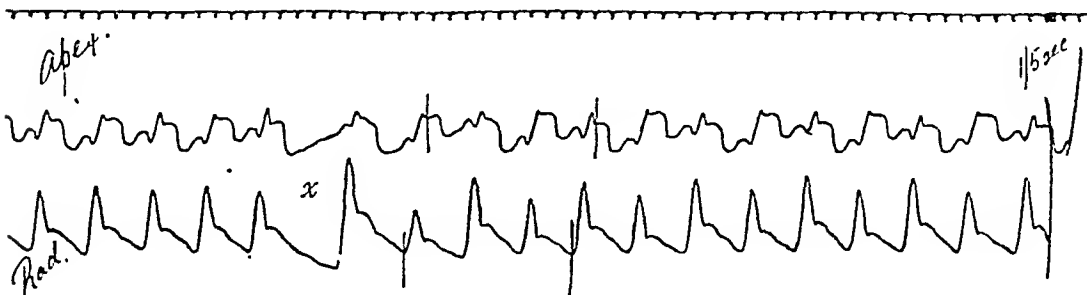


FIG. 17. Shows an increased degree of alternation succeeding the intermission; the anomalous relationship of high and low beats recurs. There is no premature beat shown in the cardiogram or radial curve during intermission.

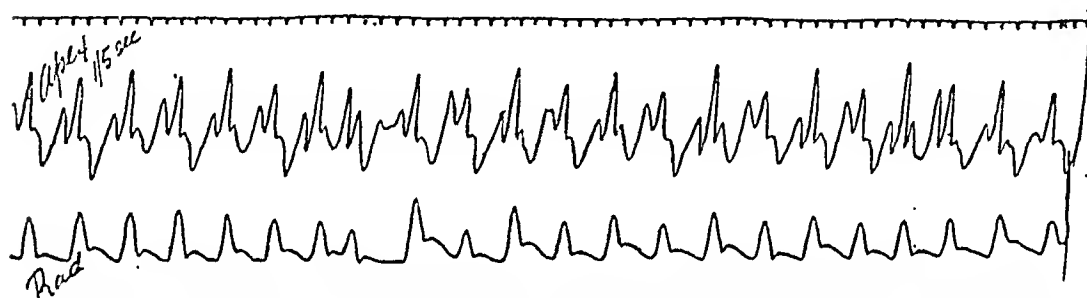


FIG. 18. Before the extra-systoles the cardiogram alternates in force, but not the radial. Succeeding the premature beat alternation is present in both curves, the height of the waves coinciding.



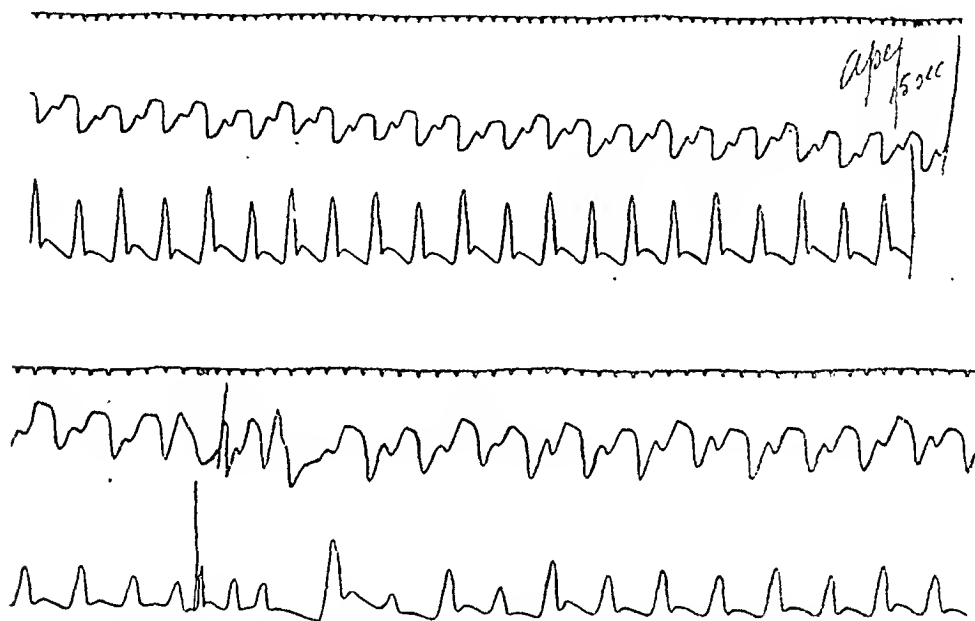
FIG. 19. Taken from the fourth space close to the edge of the sternum. The character of the cardiogram is that of right-ventricle impulse.

The irregularity did not recur at the time; later in the same day another record was taken from the same area (Fig. 18) with the cardiac and radial tambours of the G. A. Gibson polygraph. The extra-systole shows both in the cardiogram and radial pulse. Immediately before the extra-systole the cardiogram alternates in force, but there is no evidence of this in the radial.<sup>1</sup>

<sup>1</sup> Alternation in the radial pulse or an increase in its degree not uncommonly precedes extra-systole.

With the succeeding alternation in both curves the larger beat corresponds with that of the pulse, and vice versa (Figs. 16 and 17). All these curves were taken from the same spot; they are portions selected from continuous tracings, except Fig. 18, to illustrate the recurring changes in the relation of the height of the curves which were present in all observations made on many different occasions.

On moving the receiver a little to the right the shape of the cardiogram was altered (Fig. 19), being that of the right ventricle, the downstroke coinciding with the radial pulse; definite evidence of alternation is absent in the characteristic example illustrated.



FIGS. 20 and 21. Taken from the fifth intercostal space at the clinical apex beat. There is no evidence of alternation of the cardiogram in either figure.

*Tracings from the clinical apex beat.* Two records from the fifth intercostal space, 5 inches from the middle line, are shown. They were obtained on the same occasion as the other figures; in Fig. 21 the paper was going faster in order more closely to differentiate the waves; there is no evidence of alternation of the cardiogram in either figure (Figs. 20 and 21). This was the case in all the tracings taken from this area while the patent was under observation.

*Electro-cardiogram.* Fig. 22 is an electro-cardiographic record from this patient, kindly taken for me by Dr. Thos. Lewis at University College Hospital Medical School. An auricular extra-systole is shown at  $Ax$  in the radial, and at  $\frac{T}{P}$  in the electric curve. The radial pulse curve shows decided alternation; its representative  $R$  in the electric curve shows on careful measurement a very slight variation in height.

The lower waves correspond to the lower wave of the radial pulse, and vice versa, but the disparity in height is not nearly so pronounced as that of the radial pulses.

*Records of the jugular pulsation.* Evidence of alternation in the jugular pulse was not constant; frequently it was pronounced and persistent over a long record, as in Fig. 23, in which there is very decided alternation, the auricular wave corresponding in height with the radial pulse. This relationship was invariable in all tracings taken. Fig. 24 illustrates synchronous increase in the degree of alternation in the venous and arterial pulses following extra-systole.

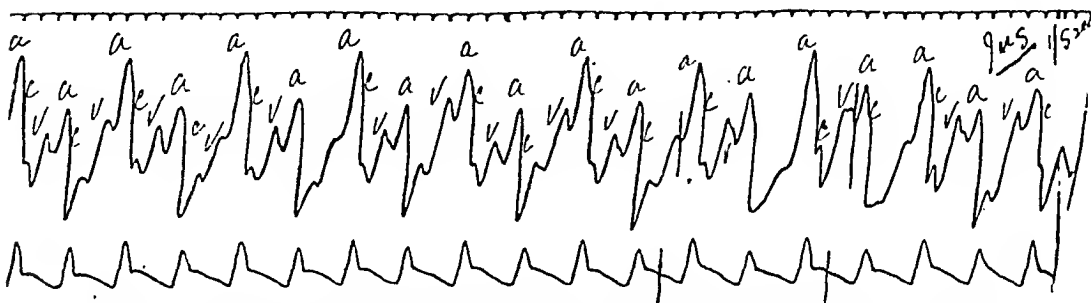


FIG. 23. Shows continuous alternation in the radial and jugular pulses; the height of the respective auricular and radial curves coincides.

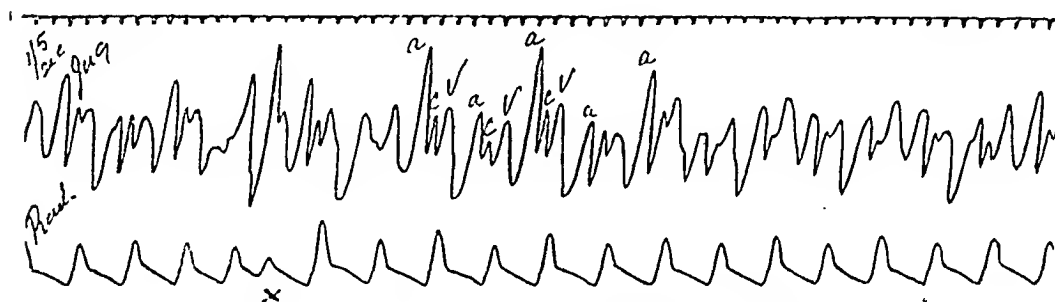


FIG. 24. Alternation in the jugular and radial pulses succeeds the extra-systole at x.

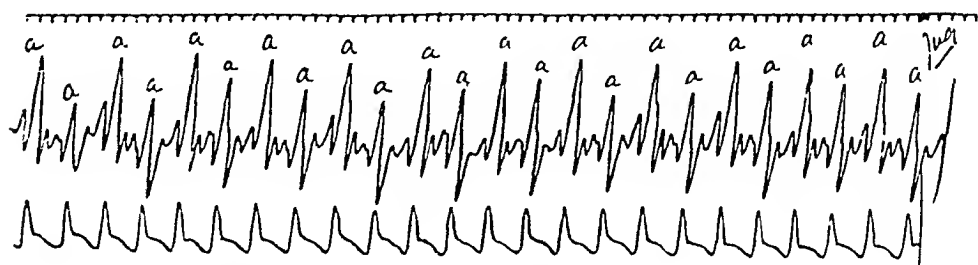


FIG. 25. The auricular curve shows decided alternation; the radial pulses are equal in height.

At times marked alternation was present in the jugular tracing, while the radial pulses were equal in force (Fig. 25).

Incidentally I mention that jugular pulsation appears to be curiously rare in *pulsus alternans*. Records were possible from five only of the twelve cases; there was no alternation evident in any of these, except in the case illustrated.

*The heart's sounds.* It is generally thought that in *pulsus alternans* the

sounds of the heart alternate in duration and intensity with the force of the pulse, and thus manifest a variation in force of the ventricular contractions. Although in this patient the alternation of the heart's impulse was decided in the area from which the records Figs. 11-17 were taken and was perceptible through the receiver, I could not make out any definite difference in the pitch or duration of the heart-sounds, or of the tricuspid murmur which was present.

The disparity in force of the radial pulses in extreme alternation is not seldom as great as that met with in recurring extra-systoles, and *a priori* we should expect the same variation in the intensity of the heart-sounds in the one case as in the other. I was, however, unable to detect any variation in the loudness or duration of the sounds corresponding to the stronger and weaker beats in any of the cases observed.

Thus in Fig. 3, in which some of the heart-beats fail to send a wave to the wrist, the heart-sounds were equally loud with the stronger and weaker beats.

In one of my cases a loud musical murmur was heard over the mitral area during systole, but its duration and characters did not change with the force of the pulse.

### *Summary.*

1. In all cases observed but one no alternation was present in records taken from the clinical apex beat, while in all disparity in force of alternate radial pulses was decided, and at times extreme. In the exceptional case the stronger beat of the heart-curve coincided with the weaker of the pulse (Fig. 1).

2. It is suggested that this anomaly is explicable on the assumption that the musculature of the ventricle producing the apex beat is not a part of that which drives the blood out of the left ventricle; otherwise it is inexplicable that the stronger beat of the ventricle should cause the weaker pulse (Fig. 1) or that ventricular contractions equal in strength, beat by beat, should cause an alternating pulse (Figs. 2-5).

3. In two patients the heart's pulsation was recorded from two distinct areas. (a) In one case the cardiograms have the character of a left and right ventricular impulse respectively. The radial pulse was markedly alternating; but there was no evidence in the cardiograms of variations in strength of the ventricular contraction.

(b) In the other case pulsation was recorded from the clinical apex beat, and also from the fourth left intercostal space about  $1\frac{1}{2}$  inches from the left edge of the sternum.

The cardiogram from both situations had the characters of left ventricular pulsation; that obtained from the fifth space at no time showed alternation in force. The cardiogram from the fourth intercostal space continuously alternated, except for brief periods. The relationships between the alternating beats of the cardiogram and those of the radial pulse were not constant, the height of the

respective waves being at times opposed, at others similar; at others, again, alternation was present in the heart-beat curve, whilst that of the radial pulse was equal; the reverse relationship occurred.

4. Alternation was often pronounced in records of the jugular pulsation of this patient; invariably the larger  $a$  wave corresponded to the higher of the radial pulse.

5. In curves having the character of right ventricular pulsation no evidence of alternation was present at any time.

6. No variation in the intensity, pitch, or duration of the heart-sounds or murmurs coincident with alternation of the pulse was detected in any case.

7. While the observations lend some support to the view of Hering, that in alternate heart-beat a partial systole of the ventricle occurs, they also show that in alternating pulse it is not always possible, in clinical cases, to determine the fact of alternating heart action.

#### REFERENCES.

1. Hering, *Prag. med. Wochenschr.*, 1904, xxix. 117, 132.
2. Hering, *Münch. med. Wochenschr.*, 1908, lv. 2. 1417.
3. Rühl, *Zeitschr. f. exp. Path. u. Ther.*, Berlin, 1906, iii. 274.
4. Volhard, *Münch. med. Wochenschr.*, 1905, lii. 1. 590.
5. Windle, *Communication to the Hunterian Society*, London, 1910.

#### DESCRIPTION OF FIGURE.

PLATE 40, FIG. 22. Simultaneous electro-cardiogram and polygraph radial curve, from the same patient as Figs. 11-21. An auricular extra-systole is shown at  $Ax$  in the radial, and at  $\frac{T}{P}$  in the electric curve. The radial pulse shows decided alternation; there is but slight variation in height of its ventricular representative  $R$  in the electric curve.



FIG. 22





# ON THE ANALYSIS OF GASTRIC CONTENTS

BY P. N. PANTON AND H. L. TIDY

THE following investigation falls into two parts: the first deals with the routine examination of test-meals in a series of cases, the second consists of an inquiry into the various methods of examining test-meals and the meaning of the results obtained.

## PART I.

All the gastric analyses conducted at the London Hospital between January 1, 1909, and August 31, 1910, are included, amounting in all to 331 cases. The cases are consecutive and in no way selected, and all test-meals sent to the Laboratory during this period are included.

*Technique.* The stomach was sometimes washed out a few hours before the test-meal was given. The test-meal was practically that of Ewald, and consisted of two large cups of tea with milk and sugar if desired and two rounds of toast lightly buttered. The gastric content was withdrawn one hour afterwards without the addition of water. It was then filtered and the filtrate and residue examined by various tests, but in the following tables we practically consider only the presence or absence of free HCl, its amount, and the measure of the total acidity. The following simple analyses were always performed:—

(1) With a portion of the filtrate Günzberg's test was performed in the usual manner. The reagent was freshly prepared for each test.

(2) To 10 c.c. of the filtrate well diluted with water three drops of dimethyl-amidoazobenzene were added and decinormal soda run in from a burette until the pink colour was converted into yellow. The original red colour passes through several shades, but with practice a definite point can in nearly every instance be recognized at which the pink colour disappears. It is this point which coincides with the neutralization of free HCl in a solution of known strength.

From the amount of decinormal soda used the amount of free acid was calculated, and is taken in our tables, when the Günzberg reaction was positive, to indicate hydrochloric acid. The meaning of the dimethyl acidity and its accuracy as a measure of free hydrochloric acid is considered in Part II.

We consider the normal dimethyl acidity to be the equivalent of 0.1 per cent. free HCl.

(3) After neutralization to dimethyl three drops of phenolphthalein were added to the same solution. Decinormal soda was run in until the first appearance of a permanent faint pink colour. (The true neutralization point is shown by the first appearance of a permanent pink.) The total acidity is given as the number of c.c. of decinormal soda which neutralize 100 c.c. of the given test meal. We find the normal total acidity varies between 40 and 50.

The analyses considered here are consecutive and were all performed by the same observers. For the arrangement and removal of the test-meals we were dependent upon numerous individuals, and it is obvious that in such a series of cases errors may occasionally arise. The mistake most likely to occur is the neglect of the rule that no medicine should be given for twelve hours previously. When some such fallacy was suspected, a second test-meal was performed when possible. One case occurred in which no free hydrochloric acid was found at the first examination and abundant free acid at the second. The patient was subsequently found to have taken a dose of bismuth from her neighbour's bottle to ease an attack of gastric pain.

The 331 cases examined are classified as follows:—

Carcinoma of stomach—43 cases, of which 30 were operated upon.

Gastric ulcer—87 cases, of which 49 were operated upon.

Duodenal ulcer—36 cases, of which 21 were operated upon.

Other gastric cases not operated upon—62 cases.

Various conditions—103 cases, of which 36 were operated upon.

### *Carcinoma of the Stomach.*

The diagnosis of carcinoma in those cases which were operated upon was confirmed in almost every instance either by the microscope or by the presence of secondary deposits. Of the thirteen cases not operated upon eight presented definite clinical evidence of carcinoma of the stomach; the remaining five were considered to be probably carcinoma. All the thirteen cases either refused operation or were considered inoperable. (See Tables I A and I B.)

In the 43 cases free hydrochloric acid was absent in 39, or in 90.7 per cent. Free hydrochloric acid when present was either above normal or but slightly decreased. The total acidity ranged from 0 to 70. The average total acidity, including the cases in which free HCl was present, is 26. In nine test-meals an appreciable dimethyl acidity was present with a negative Günzberg. The presence or absence of lactic acid we have not found particularly valuable in diagnosis.

The site of the carcinoma as shown by operation was in 3 cases the cardiac end, in 12 the pyloric end, and in the remaining 15 an intermediate position. The total acidity tended to be highest when the pylorus was affected. In cases with a very low total acidity the carcinoma was usually situated either at the cardia or in the body of the stomach and was inoperable.

A very low total acidity would seem to be an unfavourable sign; but notable exceptions occur, and very low acidities may be present with localized carcinomata at the pylorus.

The length of history was particularly inquired into in all these cases. In 30 the duration was of one year or less and no previous account of gastric symptoms could be elicited. In 4 the duration was between one and two years, in 2 between two and three years, and in 3 between three and four years. In the remaining 4 cases a definite history of gastric illness extending over a period of from twenty to thirty years was obtained, and in 3 of these cases free hydrochloric acid was present. It would therefore appear that the great majority of cases of carcinoma of the stomach have no previous history of gastric ulcer and no free hydrochloric acid in the gastric juice, whilst in the minority a history of chronic gastric ulcer can be obtained, and in such cases free hydrochloric acid usually shows no diminution. *A patient with carcinoma of the stomach and a gastric history of less than two years is almost certain to have no free HCl in the test-meal; on the other hand a patient with a gastric history of more than four years and with no free HCl is unlikely to have a carcinoma of the stomach.* In the cases of long duration, a recent history was in each instance obtained of a definite increase in the gravity of the symptoms during the preceding few months. The clinical diagnosis previous to the test-meal was carcinoma of the stomach in 34 cases.

#### *Simple Ulcer of the Stomach.*

The diagnosis was confirmed by operation in 49 cases. In a few instances in which malignancy was suspected at the operation, the simple nature of the ulcer was demonstrated by the microscope. Of the cases not operated upon all had a definite gastric history, the majority had had haematemesis, and many gave an account of several attacks extending over a number of years. It is possible that a small proportion of these cases were suffering from duodenal and not gastric ulcer, and it is possible that a few had no ulcer at all. These cases have therefore been placed in a separate table.

*Cases operated upon* (Table II A). Free hydrochloric acid was absent in five cases. In one of these a gastro-jejunostomy had previously been performed and at operation was found to be in action. In one an abscess was found opening into the stomach, and in this case free hydrochloric acid returned after operation. In one no actual ulcer was found, multiple oozing points were present (gastrostaxis), and the patient had recently lost much blood. (The relation between severe anaemia and absence of hydrochloric acid will be discussed later.) Of the remaining two cases one was an edentulous woman with the scar of an ulcer at the cardiac end, and the other was a case of dilated stomach with scarring at the pylorus. In three of the five cases exceptional circumstances were thus present.

In the remaining 44 cases free acid was present. The amount ranged

from 0.06 to 0.21, the average being 0.13. The total acidity varied from 34 to 86, the average being 58. The average total acidity and amount of free acid is thus found to be above the average, but not so far above as might be obtained from a smaller number of selected cases.

The position of the ulcer, when noted, was as follows: 28 at the pyloric end, 17 in the body, and two at the cardiac end. The average acidity was the same in the three situations. In those cases where healed ulcers only were present, the acidity was slightly lower than in the cases with active ulceration, the average total acidities being 53 and 60 respectively.

The length of history varied from a few months to many years. No difference appears in the amount of free acid and total acidity between those cases of less than one year and those of more than twenty years' duration.

The presence of recent haemorrhage, if severe, must evidently be taken into account when considering the results of test-meals in these cases. Well-marked anaemia may lead to diminution in the amount of free HCl and even to its absence, and it is a matter of clinical observation that free haemorrhage from an ulcer may be followed by temporary amelioration of the symptoms.

The clinical diagnosis previous to the test-meal was gastric ulcer in 26 cases, carcinoma in 16 cases, other conditions in 7.

*Cases not operated upon* (Table II B). Free hydrochloric acid was present in 37 out of 38 cases. In the only case in which it was absent there had been a recent severe haemorrhage and at the time the test-meal was given the haemoglobin was 20 per cent.

The average amount of free acid in the 37 cases was 0.14 per cent. and the average total acidity was 63. The averages are slightly above those in Table II B. The lower figures are naturally the more reliable.

### *Duodenal Ulcer.*

The diagnosis in 20 cases was confirmed by operation. In the remaining 15 it was made on clinical grounds and particularly on the presence of hunger pain. Melaena was absent in the majority of these cases, but was present in only one of the 20 cases operated upon.

*Cases operated upon* (Table III A). Free HCl was absent in one only of the 21 cases, a man 60 years of age. In the remaining 20 cases the free acid varied from 0.08 to 0.30, and the total acidity from 43 to 105, the averages being 0.17 and 69. The acidity, therefore, in duodenal ulcer is very considerably above normal, and appreciably above that which was found to occur in cases of gastric ulcer. A high total acidity is a very constant feature and was below 50 in only two of the 20 cases.

We may add that only one of these cases was a female, and that while haematemesis was present in five cases, definite evidence of melaena only occurred in one case.

The length of history varied from two months to nineteen years.

The clinical diagnosis previous to the test-meal was in 10 cases duodenal ulcer, in 2 gastric ulcer, in 4 carcinoma of the stomach, and in 5 other gastric conditions.

*Cases not operated upon* (Table III B). The diagnosis of these cases is naturally uncertain. Chief reliance is based upon the presence of definite hunger pain with or without melaena. Free HCl was present in all these cases. Free acid varied from 0.08 to 0.30, and the total acidity between 41 and 93, the average free acid being 0.17 and the average total acidity 68. These figures agree very closely with those in the previous table.

*Other Gastric Cases not operated upon.*

Table IV contains miscellaneous gastric conditions and is published to render the inquiry consecutive. We do not propose to discuss the various conditions in detail, but we refer to a few points of interest.

The 62 cases include two cases of achylia gastrica and two of HCl poisoning. In these free acid was absent and the total acidity very low. There were six cases of alcoholic gastritis. In five of these free acid was absent and the total acidity was low. There were 13 cases of hyperchlorhydria. These were cases with definite gastric symptoms extending from a few weeks to many years but without evidence of ulceration. All reacted to treatment. The average free acid was 0.23 and the average total acidity 86.

The remaining cases in this list consist of various conditions of 'dyspepsia', a discussion of which is beyond the scope of this paper. The only points of interest are the assistance which a test-meal affords towards making a diagnosis and the indications which it gives for treatment, the cases with a low acidity doing well with hydrochloric acid and those with a high acidity improving on alkalis. The rapidity and completeness with which such patients lose their gastric symptoms under the appropriate treatment is remarkable, and, being especially marked in those with a low acidity, becomes useful in the diagnosis from carcinoma.

In 15 cases the preliminary diagnosis was carcinoma of the stomach, and in nine of these free hydrochloric acid was present. In 15 cases the preliminary diagnosis was simple ulcer, and in five of these the acidity was distinctly below normal.

*Various Conditions. Cases operated upon.*

*Consideration of Table V.* This list includes cases in which, so far as could be discovered at operation, no gross lesion of the gastric mucous membrane was present.

In six cases carcinoma was found elsewhere than in the stomach. In four of these free HCl was present.

The remaining 31 cases include such conditions as gall-stones, gastropotosis, and appendicitis.

A preliminary diagnosis of carcinoma of the stomach was suggested in twelve of these. In six free HCl was present. Of the remaining six, in three the test-meal was obtained shortly before death, one was edentulous, and in the remaining two no cause was found for the absence of HCl.

*Various Conditions not operated upon.*

Table VI contains a large number of conditions, the majority of which had gastric symptoms, although many were never considered to be purely gastric cases. A small but interesting group of severe anaemias was purposely included. Five of these were typical examples of pernicious anaemia, and in four others the anaemia was of the secondary type. In all but one of these cases gastric secretion was practically absent. The absence of free acid after severe haemorrhage has already been referred to in dealing with gastric ulcer. In view of the theory sometimes held that pernicious anaemia is due to atony of the gastric mucous membrane it is interesting to note that a similar condition of the gastric juice is found in secondary anaemia.

In eight cases the diagnosis was neurasthenia. Five of these had acidities distinctly above the normal. In five evident malingerers the analyses agreed with the normal. Of ten cases in which the symptoms suggested carcinoma, nine gave a normal test-meal result. One of the cases referred to above had suffered from rectal haemorrhage for sixteen years. When admitted to hospital under the care of Dr. Hutchison a test-meal showed absence of HCl and a total acidity of 10. His red cells numbered 3,000,000 to the cub. mm., and his haemoglobin was 30 per cent. Nine months after a radical cure for haemorrhoids, though greatly improved in health, he still complained of dyspepsia; his blood condition had become normal, but there was still an absence of free HCl in his gastric juice. A prolonged secondary anaemia due to repeated haemorrhages seems capable of inducing a permanent atony of the gastric mucous membrane.

*Conclusions.*

1. In normal gastric contents Günzberg's reaction is positive, free hydrochloric acid varies between 0.08 and 0.12, and the acidity lies between 40 and 50.

2. In carcinoma of the stomach Günzberg's reaction is nearly always negative, i.e. free hydrochloric acid is absent. The average of the total acidity is 26. Some dimethyl acidity is often present. In the rare cases in which carcinoma is grafted upon a simple ulcer, free hydrochloric acid is usually present, and the total acidity may be normal or even above normal. Thus, in these cases, the analysis often resembles that found in simple gastric ulcer.

3. In simple gastric ulcer Günzberg's reaction is positive, the average of the free hydrochloric acid is 0.13 and the total acidity 58. Free hydrochloric acid may be absent after a severe haemorrhage or after a previous gastro-jejunostomy.

4. In duodenal ulcer the average of the free hydrochloric acid is 0.17, and the total acidity 69.

5. Free hydrochloric acid is usually absent in cases of achylia gastrica, chronic alcoholic gastritis, severe anaemia, chronic pulmonary tuberculosis, and in some forms of chronic 'dyspepsia'. In these latter cases relief of gastric symptoms usually follows treatment by acids. Cases of hyperchlorhydria are commonly relieved by alkalis.

It is not suggested that the diagnosis and treatment of gastric cases should depend upon the result of test-meals alone, but we find that the simple analysis described above affords very reliable information when taken in conjunction with clinical observation, and particularly with a carefully taken history.

TABLE I A. *Carcinoma of Stomach. Cases operated upon.*

Case 4. Total acidity: Neutral. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 9 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Scirrhus carcinoma. Site: Leather bottle. Remarks: P.M. General carcinomatosis.

Case 9. Total acidity: 24. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Present. Duration: 5 months. Previous diagnosis: Gastritis. Final diagnosis: Carcinoma. Site: Pylorus. Remarks: Carcinoma of pylorus; inoperable; carcinomatosis of peritoneum.

Case 27. Total acidity: 31. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 5 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Pylorus.

Case 32. Total acidity: (1) 8, (2) 4. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Chronic gastric ulcer. Final diagnosis: Carcinoma. Site: Body. Remarks: Inoperable: scirrhus carcinoma; body (microscope).

Case 37. Total acidity: 7. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Absent. Duration: 3 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: All stomach involved. Remarks: Inoperable.

Case 39. Total acidity: 27. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Absent. Duration: 3 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Pylorus.

Case 47. Total acidity: 4. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 1 year. Haematemesis: 4 years ago. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Scirrhus carcinoma. Site: Leather bottle. Remarks: P.M.

Case 48. Total acidity: 0. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Absent. Duration: 2 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Cardia. Remarks: Inoperable.

Case 87. Total acidity: 47. Free acid (as HCl): 0.06. Günzberg's reaction: Negative. Duration: 4 years. Previous diagnosis: Dyspepsia. Final diagnosis: Carcinoma. Site: Pylorus. Remarks: Secondary glands; microscope; inoperable.

Case 94. Total acidity: 45. Free acidity (as HCl): 0.03. Günzberg's reaction: Negative. Lactic acid: Trace. Duration: 5 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Body. Remarks: Secondaries in liver.

Case 120. Total acidity: 14. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Absent. Duration: 7 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Body. Remarks: Extensive growth; inoperable.

Case 129. Total acidity: 51. Free acid (as HCl): 0.07. Günzberg's reaction: Negative. Lactic acid: Trace. Duration: 8 months. Previous diagnosis: Carcinoma of



pylorus. Final diagnosis: Carcinoma. Site: Pylorus. Remarks: Columnar-celled carcinoma (microscope).

Case 177. Total acidity: Neutral. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 30 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Leather bottle. Remarks: Large ulcer posterior wall of stomach; no microscope.

Case 184. Total acidity: 3. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 16 months. Previous diagnosis: Duodenal ulcer. Final diagnosis: Carcinoma. Site: Pylorus. Remarks: Secondary glands; inoperable.

Case 185. Total acidity: 6. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Absent. Duration:  $2\frac{1}{2}$  years. Previous diagnosis: Carcinoma stomach. Final diagnosis: Carcinoma. Site: Cardia. Remarks: Carcinoma of oesophagus and cardia; inoperable.

Case 186. Total acidity: 41. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 30 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Pylorus.

Case 194. Total acidity: 10. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Pylorus.

Case 198. Total acidity: 48. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Present. Duration: 8 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Pylorus. Remarks: Inoperable; P.M.; chronic duodenal ulcer 1 inch beyond pylorus; large carcinoma of stomach; many secondaries.

Case 207. Total acidity: 66. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 28 years 4 months. Previous diagnosis: Gastric ulcer. Final diagnosis: Carcinoma. Site: Cardia. Remarks: 28 years' history of gastric ulcer; free for 3 years; present attack 4 months.

Case 209. Total acidity: 63. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 20 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Carcinoma. Site: Pylorus. Remarks: Progressively worse; no acute history.

Case 216. Total acidity: (1) 45, (2) 32. Free acid (as HCl): (1) 0.04, (2) Absent. Günzberg's reaction: (1, 2) Negative. Lactic acid: Present. Duration: 7 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Anterior wall. Remarks: Inoperable.

Case 230. Total acidity: (1) 26, (2) 56. Free acid (as HCl): Trace. Günzberg's reaction: Negative. Lactic acid: Absent. Duration: 10 months. Previous diagnosis: Gastric ulcer. Final diagnosis: Carcinoma. Site: Anterior wall. Remarks: Inoperable; secondary nodules.

Case 238. Total acidity: 7. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 2 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Body. Remarks: Many secondaries.

Case 297. Total acidity: (1) 28, (2) 50. Free acid (as HCl): (1) 0.03, (2) 0.08. Günzberg's reaction: (1, 2) Negative. Lactic acid: (1, 2) Absent. Duration: 4 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Pylorus.

Case 313. Total acidity: 43. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 39 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Lesser curvature. Remarks: Inoperable; fungating mass and glands; 3 months' acute history.

Case 323. Total acidity: 38. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Present. Duration:  $1\frac{1}{2}$  years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Whole stomach. Remarks: Inoperable; refused operation 8 months ago.

Case 338. Total acidity: 25. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 5 weeks. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Body.

Case 348. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration:

6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Anterior surface, lesser curvature. Remarks: Secondary in liver; inoperable; death 3 days later, haemorrhage from growth; test-meal 3 c.c. only.

Case 367. Total acidity: 16. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 7 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Pylorus. Remarks: No tumour; no haematemesis; operation; inoperable carcinoma of pylorus.

Case 369. Total acidity: 70. Free acid (as HCl): 0.105. Günzberg's reaction: Negative. Duration: 3 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma. Site: Anterior surface, greater curvature. Remarks: Secondaries in liver; inoperable.

TABLE I B. *Carcinoma of Stomach. Cases not operated upon.*

Case 25. Total acidity: 16. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 7 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Tumour considered inoperable.

Case 53. Total acidity: 11. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of pylorus. Remarks: Tumour, also nodules in liver.

Case 57. Total acidity: 9. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Dysphagia; discharged himself.

Case 63. Total acidity: 15. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Present. Duration: 1 year 6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Tumour; refused operation.

Case 84. Total acidity: 58. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Present. Duration: 1 month. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Nodule in abdominal wall—pain and vomiting; refused operation.

Case 96. Total acidity: 6. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 2 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Tumour; considered inoperable.

Case 103. Total acidity: 22. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Present. Duration: 2 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Tumour; considered inoperable.

Case 119. Total acidity: 7. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Present. Duration: 1 year. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Tumour; refused operation.

Case 148. Total acidity: 18. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 1 month. Previous diagnosis: Carcinoma of liver. Final diagnosis: Carcinoma of stomach. Remarks: Nodular liver—jaundice; discharged as inoperable.

Case 172. Total acidity: 38. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: 3 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Doubtful tumour; constant pain; no vomiting; refused operation.

Case 183. Total acidity: 26. Free acid (as HCl): 0.02. Günzberg's reaction: Negative. Duration: 1 year. Previous diagnosis: Carcinoma of pylorus. Final diagnosis: Carcinoma (probably of pylorus). Remarks: Supraclavicular glands; tumour at pylorus.

Case 244. Total acidity: 23. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Lactic acid: Absent. Duration: 9 months. Final diagnosis: Carcinoma of stomach. Remarks: Constant pain; refused operation.

Case 263. Total acidity: (1) 9, (2) 41, (3) 21. Free acid (as HCl): (1, 2, 3) Absent.

Günzberg's reaction: (1, 2, 3) Negative. Lactic acid: (1) Absent, (2) Trace, (3) Absent. Duration: 9 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of stomach. Remarks: Tumour; considered inoperable.

TABLE II A. *Simple Gastric Ulcer. Cases operated upon.*

Case 14. Total acidity: 59. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 8 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Site of ulcer: Pylorus.

Case 21. Total acidity: 21. Free acid (as HCl): 0.03. Günzberg's reaction: Negative. Duration: 5 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Cardiac ulcer (edentulous). Scar: Present.

Case 28. Total acidity: 49. Free acid (as HCl): 0.09. Günzberg's reaction: Positive. Duration: 10 years. Haematemesis: Absent. Previous diagnosis: Dilated stomach. Final diagnosis: Gastric ulcer; dilated stomach. Site of ulcer: Pylorus.

Case 50. Total acidity: 70. Free acid (as HCl): 0.20. Günzberg's reaction: Positive. Duration: 4 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus.

Case 60. Total acidity: 54. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: 2 years. Haematemesis: History. Previous diagnosis: Dilated stomach. Final diagnosis: Pyloric stenosis; dilated stomach. Scar: Present. Site of ulcer: Pylorus.

Case 66. Total acidity: 56. Free acid (as HCl): 0.16. Günzberg's reaction: Positive. Duration: 20 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Scar: Present. Site of ulcer: Pylorus.

Case 88. Total acidity: 42. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 7 months. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus.

Case 97. Total acidity: 13. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Haematemesis: Recent. Previous diagnosis: Gastric ulcer. Active ulcer: Present.

Case 110. Total acidity: 40. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 16 years. Haematemesis: Present. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus.

Case 122. Total acidity: 58. Free acid (as HCl): 0.18. Günzberg's reaction: Positive. Duration: 7 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 125. Total acidity: 51. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 6 weeks. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer. Site of ulcer: Pylorus.

Case 126. Total acidity: 51. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 5 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer; hour-glass stomach. Scar: Present. Site of ulcer: Hour-glass.

Case 128. Total acidity: 68. Free acid (as HCl): 0.20. Günzberg's reaction: Positive. Duration: 10 years. Haematemesis: History. Previous diagnosis: Dilated stomach. Final diagnosis: Gastric ulcer; dilated stomach. Scar: Present. Site of ulcer: Pylorus.

Case 134. Total acidity: 45. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 3 years. Haematemesis: Present. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer; dilated stomach. Site of ulcer: Posterior surface.

Case 135. Total acidity: 34. Free acid (as HCl): 0.06. Günzberg's reaction: Positive. Duration: 7 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Site of ulcer: Lesser curvature.

Case 176. Total acidity: 44. Free acid (as HCl): 0.07. Günzberg's reaction: Feeble. Duration: 1½ years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Site of ulcer: Lesser curvature.

Case 205. Total acidity: 66. Free acid (as HCl): 0.16. Günzberg's reaction: Positive. Duration: 9 years. Haematemesis: Absent. Previous diagnosis: Dilated stomach. Final diagnosis: Pyloric stenosis; gastric ulcer. Site of ulcer: Pylorus.

Case 206. Total acidity: 29. Günzberg's reaction: Negative. Duration: 7 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Multiple oozing points (gastrostaxis).

Case 210. Total acidity: 68. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Haematemesis: No note. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 214. Total acidity: 73. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 20 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Lesser curvature.

Case 215. Total acidity: 64. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 30 years. Haematemesis: Absent. Previous diagnosis: Gall-stones. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus.

Case 221. Total acidity: 62. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Duration: 3 years. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Posterior surface.

Case 225. Total acidity: 57. Free acid (as HCl): 0.17. Günzberg's reaction: Positive. Duration: 1 year. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Cardiac lesser curvature.

Case 227. Total acidity: 38. Free acid (as HCl): 0.09. Günzberg's reaction: Positive. Duration: 6 years. Haematemesis: Present. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus.

Case 232. Total acidity: 58. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 20 years. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer; hour-glass stomach. Site of ulcer: Hour-glass.

Case 233. Total acidity: 40. Free acid (as HCl): 0.06. Günzberg's reaction: Positive. Duration: 7 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Scar: Present. Site of ulcer: Pylorus.

Case 234. Total acidity: 58. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 4½ years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Lesser curvature.

Case 252. Total acidity: 51. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 20 years. Haematemesis: Absent. Previous diagnosis: Pyloric stenosis. Final diagnosis: Gastric ulcer. Scar: Present. Site of ulcer: Pylorus.

Case 253. Total acidity: 41. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 6 years. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer; dilated stomach. Scar: Present. Site of ulcer: Pylorus.

Case 269. Total acidity: 43. Free acid (as HCl): 0.06. Günzberg's reaction: Positive. Duration: 14 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Scar: Present. Site of ulcer: Lesser curvature.

Case 274. Total acidity: 67. Free acid (as HCl): 0.20. Günzberg's reaction: Positive. Duration: 8 years. Haematemesis: Present. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus.

Case 275. Total acidity: 47. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 19 months. Haematemesis: Absent. Previous diagnosis: Gastric

ulcer. Final diagnosis: Pyloric thickening; dilated stomach. Scar: Present. Site of ulcer: Pylorus.

Case 278. Total acidity: 74. Free acid (as HCl): 0.21. Günzberg's reaction: Positive. Duration: 5 years. Haematemesis: Absent. Previous diagnosis: Pyloric obstruction. Final diagnosis: Pyloric thickening. Scar: Present. Site of ulcer: Pylorus.

Case 279. Total acidity: 66. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 25 years. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus; lesser curvature.

Case 280. Total acidity: (1) 83, (2) 42, (3) 77. Free acid (as HCl): (1) 0.20, (2) 0.11, (3) 0.19. Günzberg's reaction: (1, 2, 3) Positive. Duration: 4 years. Haematemesis: Slight. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer and old scar. Active ulcer: Present. Scar: Present. Site of ulcer: Pylorus.

Case 283. Total acidity: 62. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 6 years. Previous diagnosis: Gastritis. Final diagnosis: Gastric ulcer. Scar: Present. Site of ulcer: Pylorus.

Case 284. Total acidity: (1) 76, (2) 61. Free acid (as HCl): (1) 0.18, (2) 0.12. Günzberg's reaction: (1, 2) Positive. Duration: 2 years. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Pyloric thickening; ulcer. Scar: Present. Site of ulcer: Pylorus.

Case 293. Total acidity: 77. Free acid (as HCl): 0.18. Günzberg's reaction: Positive. Duration: 9 months. Haematemesis: Melaena. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer, also duodenal ulcer. Active ulcer: Present. Site of ulcer: Pylorus; lesser curvature.

Case 298. Total acidity: 52. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 7 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus.

Case 300. Total acidity: 50. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Duration: 3 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus; lesser curvature.

Case 317. Total acidity: (1) 21, (2) 48. Free acid (as HCl): (1) 0.03, (2) 0.10. Günzberg's reaction: (1) Negative, (2) Positive. Duration: 3 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer; hour-glass. Remarks: (1) before operation, (2) 10 days after operation.

Case 326. Total acidity: 76. Free acid (as HCl): 0.19. Günzberg's reaction: Positive. Duration: 5 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Lesser curvature.

Case 332. Total acidity: 62. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 3 years. Haematemesis: Present. Previous diagnosis: Duodenal ulcer. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Lesser curvature.

Case 335. Total acidity: 44. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 5 years. Haematemesis: Present. Previous diagnosis: Prepyloric ulcer. Final diagnosis: Gastric ulcer; dilated stomach. Scar: Present. Site of ulcer: Lesser curvature.

Case 336. Total acidity: 46. Free acid (as HCl): 0.07. Günzberg's reaction: Tracc. Duration: 3 years. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer; hour-glass. Scar: Present. Site of ulcer: Lesser curvature.

Case 343. Total acidity: 62. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 3½ years. Haematemesis: Absent. Previous diagnosis: Pyloric obstruction. Final diagnosis: Gastric ulcer. Site of ulcer: Pylorus.

Case 353. Total acidity: 69. Free acid (as HCl): 0.17. Günzberg's reaction: Positive. Duration: 2 years. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Pyloric stenosis; simple ulcer. Scar: Present. Site of ulcer: Pylorus.

Case 368. Total acidity: 86. Free acid (as HCl): 0.16. Günzberg's reaction: Positive. Duration: 4 months. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer. Active ulcer: Present. Site of ulcer: Pylorus.

Case 371. Total acidity: 47. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Duration: 2 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer. Scar: Present. Site of ulcer: Pylorus.

TABLE II B. *Simple Gastric Ulcers. Cases not operated upon.*

Case 3. Total acidity: 85. Free acid (as HCl): 0.23. Günzberg's reaction: Positive. Duration: 6 years. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer.

Case 26. Total acidity: 55. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 4 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 42. Total acidity: 88. Free acid (as HCl): 0.22. Günzberg's reaction: Positive. Duration: 10 years and 6 months. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer; dilated stomach.

Case 59. Total acidity: 68. Free acid (as HCl): 0.17. Günzberg's reaction: Positive. Duration: 1½ years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 65. Total acidity: 65. Free acid (as HCl): 0.17. Günzberg's reaction: Positive. Duration: 2 years. Haematemesis: 2 years ago. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastric ulcer.

Case 76. Total acidity: 42. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Duration: 6 years. Haematemesis: Absent. Previous diagnosis: Dilated stomach. Final diagnosis: Gastric ulcer; dilated stomach.

Case 86. Total acidity: 55. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 9 months. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 90. Total acidity: 79. Free acid (as HCl): 0.17. Günzberg's reaction: Positive. Duration: 8 years. Haematemesis: Present. Previous diagnosis: Dilated stomach; gastric ulcer. Final diagnosis: Gastric ulcer.

Case 115. Total acidity: 56. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 3½ years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 118. Total acidity: 63. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 20 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 139. Total acidity: 63. Free acid (as HCl): 0.16. Günzberg's reaction: Positive. Duration: 2 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 140. Total acidity: 46. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 5 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 144. Total acidity: 52. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Duration: 6 months. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 146. Total acidity: 67. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Duration: 2 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 147. Total acidity: 95. Free acid (as HCl): 0.23. Günzberg's reaction: Positive. Duration: 2 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer; dilated stomach.

Case 153. Total acidity: 47. Free acid (as HCl): 0.08. Günzberg's reaction: Positive.

Duration: 2 weeks. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 155. Total acidity: 96. Free acid (as HCl): 0.22. Gönzberg's reaction: Positive. Duration: 10 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 156. Total acidity: 64. Free acid (as HCl): 0.13. Gönzberg's reaction: Positive. Duration: 1 week. Haematemesis: ? . Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 161. Total acidity: 65. Free acid (as HCl): 0.15. Gönzberg's reaction: Positive. Duration: 2 weeks. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 166. Total acidity: 56. Free acid (as HCl): 0.08. Gönzberg's reaction: Positive. Duration: 8 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 189. Total acidity: 52. Free acid (as HCl): 0.10. Gönzberg's reaction: Positive. Duration: 6 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 191. Total acidity: 49. Free acid (as HCl): 0.09. Gönzberg's reaction: Positive. Duration: 3 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 200. Total acidity: 27. Free acid (as HCl): 0.06. Gönzberg's reaction: Positive. Duration: 4 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 202. Total acidity: 48. Free acid (as HCl): 0.10. Gönzberg's reaction: Positive. Duration: 1 year. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 229. Total acidity: 69. Free acid (as HCl): 0.15. Gönzberg's reaction: Positive. Duration: 6 years. Haematemesis: Slight. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 237. Total acidity: 65. Free acid (as HCl): 0.15. Gönzberg's reaction: Positive. Duration: 3 months. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 245. Total acidity: 55. Free acid (as HCl): 0.09. Gönzberg's reaction: Positive. Duration: 10 years. Haematemesis: 10 years ago. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer; dilated stomach.

Case 246. Total acidity: 55. Free acid (as HCl): 0.09. Gönzberg's reaction: Positive. Duration: 18 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 254. Total acidity: 77. Free acid (as HCl): 0.18. Gönzberg's reaction: Positive. Duration: 1½ years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 265. Total acidity: 55. Free acid (as HCl): 0.11. Gönzberg's reaction: Positive. Duration: 15 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer; carcinoma of stomach. Final diagnosis: Gastric ulcer.

Case 270. Total acidity: 52. Free acid (as HCl): 0.12. Gönzberg's reaction: Positive. Duration: 5 years. Haematemesis: Present. Previous diagnosis: Gastritis. Final diagnosis: Gastric ulcer.

Case 288. Total acidity: 20. Free acid (as HCl): Absent. Gönzberg's reaction: Negative. Duration: 14 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 290. Total acidity: 46. Free acid (as HCl): 0.09. Gönzberg's reaction: Positive. Duration: 16 years. Haematemesis: Absent. Previous diagnosis: ? . Final diagnosis: Gastric ulcer.

Case 302. Total acidity: 78. Free acid (as HCl): 0.25. Gönzberg's reaction: Positive. Duration: 14 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 316. Total acidity: 68. Free acid (as HCl): 0.14. Güntzberg's reaction: Positive. Duration: 2 years. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 321. Total acidity: 59. Free acid (as HCl): 0.15. Güntzberg's reaction: Positive. Duration: 1 year. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 342. Total acidity: 73. Free acid (as HCl): 0.21. Güntzberg's reaction: Positive. Duration: 4 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 344. Total acidity: 61. Free acid (as HCl): 0.10. Güntzberg's reaction: Positive. Duration: 4 years. Haematemesis: Present. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastric ulcer.

Case 351. Total acidity: 65. Free acid (as HCl): 0.15. Güntzberg's reaction: Positive. Duration: 4 years. Haematemesis: Absent. Previous diagnosis: Dilated stomach. Final diagnosis: Pyloric obstruction; gastric ulcer.

### TABLE III A. *Duodenal Ulcer. Cases operated upon.*

Case 24. Sex M. Total acidity: 71. Free acid (as HCl): 0.12. Güntzberg's reaction: Positive. Duration: 1 year. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer. Active ulcer: Present. Site of ulcer: First part.

Case 29. Sex F. Total acidity: 69. Free acid (as HCl): 0.19. Güntzberg's reaction: Positive. Duration: 19 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Duodenal ulcer. Active ulcer: Present. Site of ulcer: First part.

Case 30. Sex M. Total acidity: 78. Free acid (as HCl): 0.20. Güntzberg's reaction: Positive. Duration: 2½ years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Duodenal ulcer; adhesions to gall bladder. Active ulcer: Present. Site of ulcer: First part.

Case 69. Sex M. Total acidity: 86. Free acid (as HCl): 0.14. Güntzberg's reaction: Positive. Duration: 9 months. Melaena: ?. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Duodenal ulcer.

Case 113. Sex M. Total acidity: 72. Free acid (as HCl): 0.20. Güntzberg's reaction: Positive. Duration: 3 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 114. Sex M. Total acidity: 96. Free acid (as HCl): 0.27. Güntzberg's reaction: Positive. Duration: 10 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer. Scar: Present. Site of ulcer: First part.

Case 133. Sex M. Total acidity: 62. Free acid (as HCl): 0.14. Güntzberg's reaction: Positive. Duration: 2 months. Melaena: Absent. Haematemesis: Present. Previous diagnosis: Gastric disease. Final diagnosis: Duodenal ulcer.

Case 167. Sex M. Total acidity: 72. Free acid (as HCl): 0.20. Güntzberg's reaction: Positive. Duration: 6 months. Haematemesis: Present. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Duodenal ulcer. Site of ulcer: First part.

Case 173. Sex M. Total acidity: 51. Free acid (as HCl): 0.10. Güntzberg's reaction: Positive. Duration: 3 years. Haematemesis: Present. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Duodenal ulcer.

Case 174. Sex M. Total acidity: 60. Free acid (as HCl): 0.16. Güntzberg's reaction: Positive. Duration: 6 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Dilated stomach. Final diagnosis: Duodenal ulcer.

Case 218. Sex M. Total acidity: 83. Free acid (as HCl): 0.20. Güntzberg's reaction: Positive. Duration: 2 years. Melaena: Absent. Haematemesis: Present.



Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer. Active ulcer: Present. Site of ulcer: First part.

Case 220. Sex M. Total acidity: 43. Free acid (as HCl): 0.08. Güntzberg's reaction: Positive. Duration: 7 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer. Scar: Present.

Case 224. Sex M. Total acidity: 65. Free acid (as HCl): 0.16. Güntzberg's reaction: Positive. Duration: 7 years. Haematemesis: Present. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer. Scar: Present. Site of ulcer: First part.

Case 257. Sex M. Total acidity: 73. Free acid (as HCl): 0.21. Güntzberg's reaction: Positive. Duration: 2 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Pyloric obstruction. Final diagnosis: Duodenal ulcer, first and second part. Site of ulcer: First and second part.

Case 292. Sex M. Total acidity: 53. Free acid (as HCl): 0.12. Güntzberg's reaction: Positive. Duration: 10 months. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 293. Sex M. Total acidity: 77. Free acid (as HCl): 0.18. Güntzberg's reaction: Positive. Duration: 9 months. Melaena: Present. Haematemesis: Absent. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Duodenal ulcer and gastric ulcer.

Case 299. Sex M. Total acidity: 52. Free acid (as HCl): 0.13. Güntzberg's reaction: Positive. Duration: 2½ years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer; dilated stomach.

Case 307. Sex M. Total acidity: 72. Free acid (as HCl): 0.10. Güntzberg's reaction: Trace. Duration: 10 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Gastric ulcer. Final diagnosis: Duodenal ulcer. Site of ulcer: Second part.

Case 327. Sex M. Total acidity: 63. Free acid (as HCl): 0.15. Güntzberg's reaction: Positive. Duration: 4 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer. Site of ulcer: First part.

Case 366. Sex M. Total acidity: 28. Free acid (as HCl): 0.03. Güntzberg's reaction: Negative. Duration: 5 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Dilated stomach. Final diagnosis: Duodenal ulcer; dilated stomach. Scar: Present. Site of ulcer: First part.

Case 370. Sex M. Total acidity: 105. Free acid (as HCl): 0.30. Güntzberg's reaction: Positive. Duration: 10 years. Melaena: Absent. Haematemesis: Absent. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer. Active ulcer: Present. Site of ulcer: First part.

### TABLE III B. *Duodenal Ulcer. Cases not operated upon.*

Case 43. Sex F. Total acidity: 41. Free acid (as HCl): 0.08. Güntzberg's reaction: Positive. Melaena: Present. Duration: 12 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 85. Sex M. Total acidity: 43. Free acid (as HCl): 0.19. Güntzberg's reaction: Positive. Melaena: Present. Duration: 14 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 149. Sex M. Total acidity: 56. Free acid (as HCl): 0.13. Güntzberg's reaction: Positive. Melaena: Absent. Haematemesis: Absent. Duration: 5 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Duodenal ulcer.

Case 158. Sex M. Total acidity: 68. Free acid (as HCl): 0.16. Güntzberg's reaction: Positive. Melaena: Absent. Haematemesis: Absent. Duration: 5 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Chronic duodenal ulcer.

Case 163. Sex M. Total acidity: 76. Free acid (as HCl): 0.18. Güntzberg's reaction: Positive. Melaena: Absent. Haematemesis: Absent. Duration: 2 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 243. Sex M. Total acidity: 93. Free acid (as HCl): 0.30. Günzberg's reaction: Positive. Melaena: Absent. Duration: 7 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Chronic duodenal ulcer; stenosis of pylorus.

Case 247. Sex F. Total acidity: 70. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Melaena: Absent. Duration: 6 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Duodenal ulcer.

Case 255. Sex M. Total acidity: 72. Free acid (as HCl): 0.18. Günzberg's reaction: Positive. Melaena: Present. Duration:  $1\frac{1}{4}$  years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 306. Sex M. Total acidity: 88. Free acid (as HCl): 0.19. Günzberg's reaction: Positive. Melaena: Present. Duration: 2 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 319. Sex M. Total acidity: (1) 50, (2) 56. Free acid (as HCl): (1) 0.23, (2) 0.14. Günzberg's reaction: (1, 2) Positive. Melaena: Present. Duration: 20 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 320. Sex M. Total acidity: 62. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Melaena: Absent. Duration: 12 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Duodenal ulcer.

Case 324. Sex M. Total acidity: 72. Free acid (as HCl): 0.19. Günzberg's reaction: Positive. Melaena: Absent. Duration: 20 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 340. Sex M. Total acidity: 65. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Melaena: Absent. Duration: 2 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Duodenal ulcer.

Case 353. Sex M. Total acidity: (1) 82, (2) 72. Free acid (as HCl): (1) 0.23, (2) 0.18. Günzberg's reaction: (1, 2) Positive. Melaena: Absent. Duration: 20 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

Case 360. Sex M. Total acidity: 87. Free acid (as HCl): 0.22. Günzberg's reaction: Positive. Melaena: Absent. Duration: 8 months. Previous diagnosis: Duodenal ulcer. Final diagnosis: Duodenal ulcer.

#### TABLE IV. *Other Gastric Cases. Not operated upon.*

Case 2. Total acidity: 30. Free acid (as HCl): 0.06. Günzberg's reaction: Positive. Duration: 3 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Dyspepsia.

Case 7. Total acidity: 8. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 4 years. Previous diagnosis: Enteroptosis. Final diagnosis: Achylia gastrica.

Case 8. Total acidity: 60. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 6 months. Previous diagnosis: ?. Final diagnosis: Neurotic vomiting.

Case 11. Total acidity: 23. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: 3 months. Previous diagnosis: Dyspepsia. Final diagnosis: Anaemia and dyspepsia.

Case 12. Total acidity: 85. Free acid (as HCl): 0.21. Günzberg's reaction: Positive. Duration: 7 years. Previous diagnosis: Hyperchlorhydria. Final diagnosis: Hyperchlorhydria.

Case 13. Total acidity: 66. Free acid (as HCl): 0.17. Günzberg's reaction: Positive. Duration: 2 weeks. Previous diagnosis: Dilated stomach. Final diagnosis: Hyperchlorhydria.

Case 22. Total acidity: 41. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: 1 year. Previous diagnosis: Atony of stomach. Final diagnosis: Dilated stomach.

Case 34. Total acidity: 62. Free acid (as HCl): 0.12. Günzberg's reaction: Positive. Duration: 3 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Alcoholic gastritis.

Case 35. Total acidity: 71. Free acid (as HCl): 0.15. Günzberg's reaction:

Positive. Duration: 9 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Dyspepsia.

Case 44. Total acidity: 45. Free acid (as HCl): 0.12. Güntzberg's reaction: Positive. Duration: 2 years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Gastritis.

Case 45. Total acidity: 12. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 1 year. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Chronic alcoholic gastritis.

Case 46. Total acidity: 9. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 3 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Chronic alcoholic gastritis.

Case 54. Total acidity: 56. Free acid (as HCl): 0.14. Güntzberg's reaction: Positive. Duration: 6 months. Previous diagnosis: Hyperchlorhydria. Final diagnosis: Gastralgia.

Case 67. Total acidity: 66. Free acid (as HCl): 0.18. Güntzberg's reaction: Positive. Duration: 1 week. Previous diagnosis: Dyspepsia. Final diagnosis: Acute gastritis.

Case 68. Total acidity: 114. Free acid (as HCl): 0.30. Güntzberg's reaction: Positive. Duration: 4 years. Previous diagnosis: ?. Final diagnosis: Hyperchlorhydria.

Case 79. Total acidity: 28. Free acid (as HCl): 0.01. Güntzberg's reaction: Negative. Duration: 5 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastritis.

Case 80. Total acidity: 60. Free acid (as HCl): 0.20. Güntzberg's reaction: Positive. Duration: 2 weeks. Previous diagnosis: ?. Final diagnosis: Acute gastritis.

Case 83. Total acidity: 60. Free acid (as HCl): 0.13. Güntzberg's reaction: Positive. Duration: 9 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastritis.

Case 92. Total acidity: 30. Free acid (as HCl): 0.02. Güntzberg's reaction: Negative. Duration: 6 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Chronic gastritis (edentulous).

Case 93. Total acidity: 20. Free acid (as HCl): 0.04. Güntzberg's reaction: Negative. Duration: 12 years. Previous diagnosis: Chronic gastritis. Final diagnosis: Chronic gastritis.

Case 95. Total acidity: 16. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 5 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Chronic alcoholic gastritis.

Case 98. Total acidity: 43. Free acid (as HCl): 0.11. Güntzberg's reaction: Positive. Duration: 6 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastritis.

Case 104. Total acidity: 77. Free acid (as HCl): 0.24. Güntzberg's reaction: Positive. Duration: 1 year. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Hyperchlorhydria.

Case 105. Total acidity: 85. Free acid (as HCl): 0.27. Güntzberg's reaction: Positive. Duration: 2 weeks. Previous diagnosis: Gastric ulcer. Final diagnosis: Hyperchlorhydria.

Case 106. Total acidity: 51. Free acid (as HCl): 0.12. Güntzberg's reaction: Positive. Duration: 2 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastralgia.

Case 116. Total acidity: 21. Free acid (as HCl): 0.01. Güntzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Chronic gastritis. Final diagnosis: Alcoholic gastritis.

Case 142. Total acidity: 43. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 4 years. Previous diagnosis: Dilated stomach. Final diagnosis: Dilated stomach.

Case 143. Total acidity: 11. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 5 weeks. Previous diagnosis: HCl poisoning. Final diagnosis: HCl poisoning.

Case 151. Total acidity: (1) 19, (2) 43. Free acid (as HCl): (1, 2) Absent. Güntzberg's

reaction: (1, 2) Negative. Duration: 5 months. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastritis.

Case 157. Total acidity: 13. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 5 years. Previous diagnosis: Hyperchlorhydria. Final diagnosis: Chronic alcoholic gastritis (edentulous).

Case 159. Total acidity: 44. Free acid (as HCl): 0.12. Günzberg's reaction: Positive. Duration: 5 years. Previous diagnosis: Persistent vomiting. Final diagnosis: Dilated stomach.

Case 162. Total acidity: 77. Free acid (as HCl): 0.24. Günzberg's reaction: Positive. Duration: 3 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Hyperchlorhydria.

Case 164. Total acidity: 46. Free acid (as HCl): Trace. Günzberg's reaction: Negative. Duration: 10 years. Previous diagnosis: Dilated stomach. Final diagnosis: Dilated stomach.

Case 165. Total acidity: 37. Free acid (as HCl): 0.07. Günzberg's reaction: Positive. Duration: 7 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Chronic gastritis.

Case 187. Total acidity: 84. Free acid (as HCl): 0.17. Günzberg's reaction: Positive. Duration: 7 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Hyperchlorhydria.

Case 188. Total acidity: 45. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration:  $1\frac{1}{2}$  years. Previous diagnosis: Edentulous dyspepsia. Final diagnosis: Chronic gastritis (edentulous).

Case 192. Total acidity: 50. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 11 years. Previous diagnosis: Chronic gastritis. Final diagnosis: Chronic gastritis.

Case 197. Total acidity: (1) 45, (2) 40. Free acid (as HCl): (1) Absent, (2) 0.05. Günzberg's reaction: (1, 2) Negative. Duration: 3 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Chronic gastritis.

Case 204. Total acidity: 46. Free acid (as HCl): 0.12. Günzberg's reaction: Positive. Duration: 3 months. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastralgia.

Case 219. Total acidity: 38. Free acid (as HCl): 0.07. Günzberg's reaction: Positive. Duration:  $1\frac{1}{2}$  years. Previous diagnosis: Gastritis. Final diagnosis: Chronic gastritis.

Case 223. Total acidity: 44. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 4 years. Previous diagnosis: Gastritis. Final diagnosis: Chronic gastritis.

Case 226. Total acidity: 78. Free acid (as HCl): 0.20. Günzberg's reaction: Positive. Duration: 3 years. Previous diagnosis: Gastritis. Final diagnosis: Hyperchlorhydria.

Case 236. Total acidity: 61. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 4 years. Previous diagnosis: Hyperchlorhydria. Final diagnosis: Gastralgia.

Case 240. Total acidity: 58. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration:  $1\frac{1}{2}$  years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Edentulous dyspepsia.

Case 242. Total acidity: 36. Free acid (as HCl): 0.07. Günzberg's reaction: Positive. Duration: 6 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Chronic gastritis.

Case 247. Total acidity: 23. Free acid (as HCl): 0.05. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Edentulous dyspepsia.

Case 249. Total acidity: 44. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 8 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastralgia.

Case 250. Total acidity: 46. Free acid (as HCl): 0.09. Günzberg's reaction:

Positive. Duration: 20 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastritis.

Case 251. Total acidity: 47. Free acid (as HCl): 0.07. Günzberg's reaction: Positive. Duration: 4 years. Previous diagnosis: Acid dyspepsia. Final diagnosis: Gastralgia.

Case 262. Total acidity: 64. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 9 months. Previous diagnosis: Duodenal ulcer. Final diagnosis: Gastritis.

Case 271. Total acidity: 89. Free acid (as HCl): 0.22. Günzberg's reaction: Positive. Duration: 1 year. Previous diagnosis: Gastric ulcer. Final diagnosis: Hyperchlorhydria.

Case 286. Total acidity: 22. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 7 years. Previous diagnosis: Achylia gastrica. Final diagnosis: Achylia gastrica.

Case 304. Total acidity: 14. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 7 months. Previous diagnosis: Gastritis. Final diagnosis: Chronic gastritis (edentulous).

Case 305. Total acidity: 113. Free acid (as HCl): 0.365. Günzberg's reaction: Positive. Duration: Many years. Previous diagnosis: Dyspepsia. Final diagnosis: Hyperchlorhydria.

Case 325. Total acidity: 16. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 3 weeks. Previous diagnosis: HCl poisoning. Final diagnosis: HCl poisoning.

Case 329. Total acidity: 37. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 2 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastritis (edentulous).

Case 333. Total acidity: 94. Free acid (as HCl): 0.27. Günzberg's reaction: Positive. Duration: 6 weeks. Previous diagnosis: Gastric ulcer. Final diagnosis: Hyperchlorhydria.

Case 337. Total acidity: 79. Free acid (as HCl): 0.17. Günzberg's reaction: Positive. Duration: Many years. Previous diagnosis: ?. Final diagnosis: Hyperchlorhydria.

Case 339. Total acidity: 54. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 2 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastralgia.

Case 341. Total acidity: 68. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 7 months. Present diagnosis: Achylia gastrica. Final diagnosis: Gastralgia.

Case 349. Total acidity: 49. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 2 weeks. Present diagnosis: Gastro-enteritis. Final diagnosis: Gastro-enteritis.

Case 355. Total acidity: 79. Free acid (as HCl): 0.19. Günzberg's reaction: Positive. Duration: 4 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Hyperchlorhydria.

#### TABLE V. *Various Conditions. Cases operated upon.*

Case 1. Total acidity: 46. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 5 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastroptosis.

Case 19. Total acidity: 10. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 weeks. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gall-stones.

Case 23. Total acidity: 73. Free acid (as HCl): 0.16. Günzberg's reaction:

Positive. Duration: 1 year. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gall-stones.

Case 31. Total acidity: 32. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: 4½ months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Nothing found.

Case 52. Total acidity: 37. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 4 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of splenic flexure.

Case 56. Total acidity: 61. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 15 months. Previous diagnosis: Carcinoma of rectum. Final diagnosis: Carcinoma of rectum.

Case 61. Total acidity: 55. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 9 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Nothing found.

Case 71. Total acidity: 5. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 2 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Trichiniasis.

Case 72. Total acidity: 40. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 3 years. Previous diagnosis: Gastric disease. Final diagnosis: Long transverse colon.

Case 75. Total acidity: 34. Free acid (as HCl): 0.07. Günzberg's reaction: Positive. Duration: 12 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gall-stones.

Case 78. Total acidity: 53. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: Some years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Chronic pancreatitis.

Case 82. Total acidity: 76. Free acid (as HCl): 0.21. Günzberg's reaction: Positive. Duration: Years. Previous diagnosis: Gastropotosis. Final diagnosis: Gastropotosis.

Case 99. Total acidity: 83. Free acid (as HCl): 0.24. Günzberg's reaction: Positive. Duration: 5 weeks. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of sigmoid.

Case 100. Total acidity: 4. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 4 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Chronic peritonitis.

Case 108. Total acidity: 36. Free acid (as HCl): 0.05. Günzberg's reaction: Positive. Duration: 3 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gall-stones.

Case 109. Total acidity: 23. Free acid (as HCl): 0.05. Günzberg's reaction: Negative. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastropotosis.

Case 112. Total acidity: 49. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 5 years. Previous diagnosis: Gastropotosis. Final diagnosis: Gastropotosis.

Case 117. Total acidity: 36. Free acid (as HCl): 0.09. Günzberg's reaction: Positive. Duration: 2 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Nothing found.

Case 121. Total acidity: 10. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 5 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Pulmonary tuberculosis.

Case 130. Total acidity: 40. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 2 years. Final diagnosis: Gall-stones.

Case 131. Total acidity: 13. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 3 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Suppurative cholangitis and gall-stones.

Case 136. Total acidity: 48. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 1 year. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of transverse colon.

Case 168. Total acidity: 90. Free acid (as HCl): 0.21. Günzberg's reaction: Positive. Duration: 7 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Appendicitis.

Case 171. Total acidity: 39. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of transverse colon.

Case 179. Total acidity: 50. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 7 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Gastropptosis.

Case 211. Total acidity: 50. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Previous diagnosis: Gastric ulcer. Final diagnosis: Gall-stones.

Case 213. Total acidity: 52. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Duration: 12 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Appendicitis.

Case 277. Total acidity: 45. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 10 weeks. Previous diagnosis: Duodenal ulcer. Final diagnosis: Nothing found.

Case 281. Total acidity: 57. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 2 years. Previous diagnosis: Hour-glass stomach. Final diagnosis: Gastropptosis.

Case 282. Total acidity: 52. Free acid (as HCl): 0.09. Günzberg's reaction: Positive. Duration: 3 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Gall-stones.

Case 294. Total acidity: 53. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 20 years. Previous diagnosis: Gall-stones. Final diagnosis: Gall-stones.

Case 305. Total acidity: 84. Free acid (as HCl): 0.22. Günzberg's reaction: Positive. Duration: 2 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Appendicitis.

Case 308. Total acidity: 42. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Carcinoma of pancreas. Final diagnosis: Stenosis of bile duct.

Case 312. Total acidity: 57. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 8 months. Previous diagnosis: Gastric ulcer. Final diagnosis: Nothing found.

Case 328. Total acidity: 33. Günzberg's reaction: Negative. Duration: 7 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Carcinoma of duodeno-jejunal flexure.

Case 345. Total acidity: 53. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Previous diagnosis: Appendicular dyspepsia. Final diagnosis: Nothing found.

Case 357. Total acidity: 66. Free acid (as HCl): 0.21. Günzberg's reaction: Positive. Duration: 7 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Appendicitis.

#### TABLE VI. *Various Conditions. Not operated upon.*

Case 6. Total acidity: 58. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Cirrhosis of liver.

Case 8. Total acidity: 60. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 6 months. Previous diagnosis: ?. Final diagnosis: Neurotic vomiting.

Case 10. Total acidity: 76. Free acid (as HCl): Present. Günzberg's reaction: Positive. Duration: 4 months. Final diagnosis: Enteropptosis.

Case 11. Total acidity: 23. Free acid (as HCl): 0.04. Günzberg's reaction: Nega-

tive. Duration: 3 months. Previous diagnosis: Dyspepsia. Final diagnosis: Anacmia and dyspepsia.

Case 16. Total acidity: 33. Free acid (as HCl): 0.05. Günzberg's reaction: Negative. Previous diagnosis: Mucous colitis. Final diagnosis: Mucous colitis.

Case 18. Total acidity: 36. Free acid (as HCl): 0.02. Günzberg's reaction: Negative. Duration: 2 weeks. Previous diagnosis: Vomiting. Final diagnosis: Acute haemorrhagic nephritis.

Case 20. Total acidity: 39. Free acid (as HCl): Present. Günzberg's reaction: Positive. Duration: 2 years. Previous diagnosis: Dyspepsia. Final diagnosis: Neurasthenia.

Case 36. Total acidity: 8. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 4 years 2 weeks. Previous diagnosis: Pernicious anaemia. Final diagnosis: Pernicious anaemia.

Case 38. Total acidity: 48. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 5 years. Previous diagnosis: ?. Final diagnosis: Nil (malingerer).

Case 41. Total acidity: 44. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: 7 months. Previous diagnosis: Carcinoma of oesophagus. Final diagnosis: Functional.

Case 49. Total acidity: 65. Free acid (as HCl): 0.15. Günzberg's reaction: Positive. Duration: 15 years. Previous diagnosis: Neurasthenia. Final diagnosis: Neurasthenia.

Case 64. Total acidity: 56. Free acid (as HCl): 0.12. Günzberg's reaction: Positive. Duration: 8 months. Previous diagnosis: Dilated stomach. Final diagnosis: Nil (malingerer).

Case 70. Total acidity: 45. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: 10 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Neurasthenia.

Case 74. Total acidity: 41. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 8 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gastroptosis.

Case 77. Total acidity: 14. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 2 years. Previous diagnosis: Mucous colitis. Final diagnosis: Mucous colitis.

Case 81. Total acidity: 38. Free acid (as HCl): 0.08. Günzberg's reaction: Positive. Duration: 1 year. Previous diagnosis: Lumbago. Final diagnosis: Lumbago.

Case 89. Total acidity: 43. Free acid (as HCl): 0.06. Günzberg's reaction: Positive. Previous diagnosis: ?. Final diagnosis: Nil (malingerer).

Case 111. Total acidity: 33. Free acid (as HCl): 0.05. Günzberg's reaction: Negative. Duration: 1 year. Previous diagnosis: Carcinoma of pancreas. Final diagnosis: Cirrhosis of liver.

Case 123. Total acidity: Nil. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Pernicious anaemia. Final diagnosis: Pernicious anaemia.

Case 124. Total acidity: 29. Free acid (as HCl): 0.02. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Ulcerative colitis. Final diagnosis: Ulcerative colitis.

Case 138. Total acidity: 42. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 6 months. Previous diagnosis: Colitis. Final diagnosis: Colitis.

Case 141. Total acidity: 62. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 1 year. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Neurasthenia.

Case 150. Total acidity: 41. Free acid (as HCl): 0.04. Günzberg's reaction: Positive. Duration: 6 weeks. Previous diagnosis: Chlorosis. Final diagnosis: Chlorosis.

Case 152. Total acidity: 37. Free acid (as HCl): 0.05. Günzberg's reaction: Negative. Previous diagnosis: Gastroptosis. Final diagnosis: Gastroptosis.

Case 169. Total acidity: 48. Free acid (as HCl): 0.12. Günzberg's reaction: Positive. Previous diagnosis: Dilated stomach. Final diagnosis: Dementia.

Case 170. Total acidity: 66. Free acid (as HCl): 0.10. Günzberg's reaction:



Positive. Duration: 3 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Constipation.

Case 180. Total acidity: (1) 29, (2) 30. Free acid (as HCl): (1) 0.06, (2) 0.08. Günzberg's reaction: (1, 2) Positive. Previous diagnosis: Chronic gastric ulcer. Final diagnosis: Neurasthenia.

Case 182. Total acidity: 13. Free acid (as HCl): 0.02. Günzberg's reaction: Negative. Duration: 3 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Enteroptosis.

Case 190. Total acidity: 37. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 2 weeks. Previous diagnosis: Gastritis. Final diagnosis: Pulmonary tuberculosis with gastritis.

Case 193. Total acidity: 43. Free acid (as HCl): Absent. Günzberg's reaction: Positive. Duration: 6 months. Previous diagnosis: Pernicious anaemia. Final diagnosis: Pernicious anaemia (test-meal, 8 c.c. only).

Case 195. Total acidity: 7. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Pernicious anaemia. Final diagnosis: Pernicious anaemia.

Case 199. Total acidity: 10. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Anaemia. Final diagnosis: Anaemia secondary to haemorrhage.

Case 212. Total acidity: 60. Free acid (as HCl): 0.14. Günzberg's reaction: Positive. Duration: 2 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Tabes.

Case 222. Total acidity: 70. Free acid (as HCl): 0.21. Günzberg's reaction: Positive. Duration: 5 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Neurasthenia.

Case 235. Total acidity: 23. Free acid (as HCl): Absent. Günzberg's reaction: Negative. Duration: 7 months. Previous diagnosis: Anaemia. Final diagnosis: Severe secondary anaemia.

Case 239. Total acidity: 70. Free acid (as HCl): 0.18. Günzberg's reaction: Positive. Duration: 10 years. Previous diagnosis: Gastropnoia. Final diagnosis: Neurasthenia.

Case 241. Total acidity: 55. Free acid (as HCl): 0.12. Günzberg's reaction: Positive. Duration: 4 months. Previous diagnosis: Nervous vomiting. Final diagnosis: Nervous vomiting.

Case 256. Total acidity: 31. Free acid (as HCl): 0.05. Günzberg's reaction: Negative. Duration: 6 months. Previous diagnosis: Secondary anaemia. Final diagnosis: Anaemia secondary to haemorrhage.

Case 258. Total acidity: 60. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 5 weeks. Previous diagnosis: Gastritis. Final diagnosis: Dementia.

Case 259. Total acidity: 49. Free acid (as HCl): 0.11. Günzberg's reaction: Positive. Duration: 8 weeks. Previous diagnosis: Gastritis. Final diagnosis: Senile dementia.

Case 260. Total acidity: 60. Free acid (as HCl): 0.13. Günzberg's reaction: Positive. Duration: 3 years. Previous diagnosis: Dilated stomach. Final diagnosis: Enteroptosis.

Case 261. Total acidity: 34. Free acid (as HCl): 0.06. Günzberg's reaction: Positive. Duration: 1½ years. Previous diagnosis: Gastric ulcer. Final diagnosis: Chlorosis.

Case 264. Total acidity: 28. Free acid (as HCl): 0.04. Günzberg's reaction: Negative. Duration: Years. Previous diagnosis: Duodenal ulcer. Final diagnosis: Cirrhosis of liver.

Case 266. Total acidity: 54. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 1 year. Previous diagnosis: Gastric ulcer. Final diagnosis: Neurosis.

Case 267. Total acidity: (1) 3, (2) 9. Free acid (as HCl): (1, 2) Absent. Günzberg's reaction: (1, 2) Negative. Previous diagnosis: Duodenal ulcer. Final diagnosis: Secondary anaemia, cirrhosis of liver.

Case 268. Total acidity: 44. Free acid (as HCl): 0.09. Günzberg's reaction: Positive. Duration: 1 year. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Debility.

Case 273. Total acidity: 47. Free acid (as HCl): 0.10. Günzberg's reaction: Positive. Duration: 7 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Chronic constipation.

Case 285. Total acidity: 50. Free acid (as HCl): 0.13. Güntzberg's reaction: Positive. Duration: 7 years. Previous diagnosis: Gastritis. Final diagnosis: Functional.

Case 287. Total acidity: 55. Free acid (as HCl): 0.12. Güntzberg's reaction: Positive. Duration: 6 months. Previous diagnosis: Pyloric obstruction. Final diagnosis: Functional.

Case 289. Total acidity: 34. Free acid (as HCl): 0.06. Güntzberg's reaction: Positive. Duration: 8 months. Previous diagnosis: Gastritis. Final diagnosis: Pulmonary tuberculosis and gastritis.

Case 291. Total acidity: 79. Free acid (as HCl): 0.20. Güntzberg's reaction: Positive. Duration: Years. Previous diagnosis: Pyloric obstruction. Final diagnosis: Functional.

Case 296. Total acidity: 22. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 1 year. Previous diagnosis: Cirrhosis of liver. Final diagnosis: Cirrhosis of liver; delirium tremens.

Case 301. Total acidity: 49. Free acid (as HCl): 0.10. Güntzberg's reaction: Positive. Duration: 1 year. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Appendicitis.

Case 309. Total acidity: 65. Free acid (as HCl): 0.16. Güntzberg's reaction: Positive. Duration: 6 months. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Gall-stones.

Case 310. Total acidity: (1) 59, (2) 44. Free acid (as HCl): (1, 2) Absent. Güntzberg's reaction: (1, 2) Negative. Duration: Years. Previous diagnosis: Gastroparesis. Final diagnosis: Migraine.

Case 311. Total acidity: 49. Free acid (as HCl): 0.12. Güntzberg's reaction: Positive. Duration: 3 years. Previous diagnosis: Gastritis. Final diagnosis: Nil (malingerer).

Case 334. Total acidity: 13. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 12 years and 1 year. Previous diagnosis: Cirrhosis of liver. Final diagnosis: Cirrhosis of liver.

Case 346. Total acidity: 54. Free acid (as HCl): 0.11. Güntzberg's reaction: Positive. Duration: 5 years. Previous diagnosis: Banti's disease. Final diagnosis: Banti's disease.

Case 347. Total acidity: 50. Free acid (as HCl): 0.10. Güntzberg's reaction: Positive. Previous diagnosis: Gastric ulcer. Final diagnosis: Nil (malingerer).

Case 350. Total acidity: 85. Free acid (as HCl): 0.22. Güntzberg's reaction: Positive. Duration: 6 years. Previous diagnosis: Gastritis. Final diagnosis: Neurasthenia.

Case 352. Total acidity: 20. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 1 year. Previous diagnosis: Cirrhosis of liver. Final diagnosis: Cirrhosis of liver.

Case 354. Total acidity: 62. Free acid (as HCl): 0.12. Güntzberg's reaction: Positive. Duration: 17 years. Previous diagnosis: Mucous colitis. Final diagnosis: Mucous colitis.

Case 356. Total acidity: 55. Free acid (as HCl): 0.13. Güntzberg's reaction: Positive. Duration: 6 weeks. Previous diagnosis: Gastritis. Final diagnosis: Constipation.

Case 362. Total acidity: 48. Free acid (as HCl): 0.11. Güntzberg's reaction: Positive. Duration: 6 years. Previous diagnosis: Carcinoma of stomach. Final diagnosis: Constipation.

Case 364. Total acidity: 6. Free acid (as HCl): Absent. Güntzberg's reaction: Negative. Duration: 1 year. Previous diagnosis: Pernicious anaemia. Final diagnosis: Pernicious anaemia.

Case 365. Total acidity: 53. Free acid (as HCl): 0.11. Güntzberg's reaction: Positive. Duration: 5 years. Previous diagnosis: Gastric ulcer. Final diagnosis: Enteroptosis.

## PART II.

Those who are concerned with the chemical examination of gastric contents have at their disposal a considerable variety of methods of examination, which differ both in their technique and in the information which they yield. The method which should most commend itself is one which is reasonably accurate, simple in accomplishment, and which affords the greatest possible information for diagnosis and treatment. The methods most commonly employed in this country are the following:—The Prout-Winter method, Töpfer's method, the inversion of cane-sugar, and Volhard's method, or one of its modifications.

The amount of free HCl and protein-HCl as estimated by the Prout-Winter method has been shown by Willcox to be extremely inaccurate. The method depends upon the fallacy that HCl in an organic mixture is volatilized by heating to dryness. Willcox has shown, and we have confirmed his observation, that only about one-third of free HCl is thus driven off. The amount of protein-HCl is proportionately over-estimated. We have investigated as far as possible the relative values of the remaining three methods, from the point of view both of their accuracy and of the information which they give.

The diagnostic value of the various methods seemed to us to be best estimated by examining a series of test-meals by them all. In the following table fifty-two test-meals from various gastric conditions chosen indiscriminately were analysed in this manner. Certain other examinations shown in the table will be referred to later.

TABLE VII. *Examination of Gastric Contents by Various Methods.*

Total Acidity. Phenol- phthalein.	Dimethyl Acidity.	Günzberg's Reaction.	'Active HCl.' Vol- hard.	'Free HCl.' Inversion of Cane Sugar.	After Extraction with Ether.		Total Nitrogen (grammes %).
					Total Acidity. Phenol- phthalein.	Dimethyl Acidity.	
1. 58 } 0.21 }	0.14	Positive	0.25	0.15	—	—	—
2. 45 } 0.16 }	0.09	Positive	0.22	0.10	—	—	—
3. 47 } 0.17 }	0.116	Positive	0.19	0.135	—	—	—
4. 51 } 0.186 }	0.127	Positive	0.24	0.126	—	—	—
5. 72 } 0.262 }	0.204	Positive	0.219	0.171	—	—	—
6. 36 } 0.131 }	0.075	Positive	0.073	0.036	—	—	—
7. 50 } 0.182 }	0.116	Positive	0.113	0.061	—	—	—

NOTES.—1. Edentulous dyspepsia. 3. Operation. Chronic gastric ulcer (pylorus). 4. Dyspepsia. 5. Operation. Duodenal ulcer. 6. Dyspepsia. 7. Operation. Gall-stones. Stomach normal.

TABLE VII (continued).

Total Acidity. Phenol- phthalein.	Dimethyl Acidity.	Günzberg's Reaction.	'Active HCl.' Vol- hard.	'Free HCl.' Inversion of Cane Sugar.	After Extraction with Ether.		Total Nitrogen (grammes %).
					Total Acidity. Phenol- phthalein.	Dimethyl Acidity.	
8. 83 } 0.303 }	0.204	Positive	—	0.167	73 } 0.266 }	0.182	—
9. 55 } 0.200 }	0.091	Positive	0.20	0.051	46 } 0.167 }	0.065	—
10. 36 } 0.131 }	0.04	Very faint	0.156	0.008	30 } 0.108 }	0.020	0.140
11. 76 } 0.277 }	0.21	Positive	0.288	—	65 } 0.236 }	0.18	—
12. 43 } 0.157 }	0.091	Positive	0.113	—	39 } 0.142 }	0.080	—
13. 45 } 0.164 }	0.10	Positive	0.196	0.04	42 } 0.153 }	0.077	—
14. 47 } 0.169 }	0.10	Positive	0.164	—	45 } 0.164 }	0.087	—
15. 37 } 0.135 }	0.06	Positive	0.07	—	—	—	—
16. 41 } 0.149 }	0.043	Positive	0.132	0.036	—	—	—
17. 28 } 0.102 }	0.025	Negative	0.143	Absent	—	—	—
18. 44 } 0.160 }	0.116	Positive	0.142	0.119	—	—	—
19. 56 } 0.203 }	0.131	Positive	0.219	0.066	—	—	—
20. 50 } 0.182 }	0.036	Negative	0.069	Absent	44 } 0.160 }	0.021	—
21. 70 } 0.255 }	0.105	Negative	0.222	?	38 } 0.140 }	0.091	—
22. 95 } 0.346 }	0.233	Positive	—	0.222	—	—	0.321
23. 60 } 0.219 }	0.160	Positive	—	0.098	—	—	0.198
24. 77 } 0.281 }	0.240	Positive	—	0.231	—	—	0.309
25. 66 } 0.240 }	0.168	Positive	0.248	0.163	—	—	—
26. 52 } 0.187 }	0.094	Positive	0.204	0.041	—	—	—
27. 28 } 0.102 }	0.029	Negative	0.120	—	—	—	—
28. 13 } 0.047 }	Absent	Negative	0.069	—	—	—	—
29. 56 } 0.204 }	0.138	Positive	0.213	0.104	—	—	—

NOTES.—8. Operation. Chronic gastric ulcer (pylorus). 9. Gastric ulcer. 10. Chronic gastritis. 11. Operation. Gastric ulcer (pylorus). 12. Operation. Duodenal ulcer (scar). 13. Chronic dyspepsia. 14. Gastric ulcer. 15. Chronic gastritis. 16. Anaemia. 18. Dilated stomach. 19. Duodenal ulcer. 20. Chronic gastritis. 21. Carcinoma of the stomach. Secondaries in the liver. Inoperable. 22, 23, and 24. Gastric ulcer. 25. Operation. Chronic gastric ulcer. Stenosis of the pylorus. 26. Operation. Adhesions round the gall bladder. Stomach and appendix normal. 27. Dyspepsia. 28. Chronic alcoholic gastritis. 29. Duodenal ulcer.

TABLE VII (*continued*).

Total Acidity. Phenol- phthalein.	Dimethyl Acidity.	Günzberg's Reaction.	'Active HCl.' Vol- hard.	'Free HCl.' Inversion of Cane Sugar.	After Extraction with Ether.		Total Nitrogen (grammes %).
					Total Acidity. Phenol- phthalein.	Dimethyl Acidity.	
30. 59) 0.215)	0.091	Negative	0.171	—	50) 0.182)	0.077	—
31. 63) 0.226)	0.154	Positive	0.22	0.086(?)	—	—	—
32. 94) 0.343)	0.270	Positive	0.346	0.270	—	—	—
33. 20) 0.073)	Absent	Negative	0.074	—	—	—	—
34. 56) 0.204)	0.043	Negative	0.175	—	—	—	—
35. 44) 0.160)	0.046	Negative	0.179	—	—	—	—
36. 70) 0.179)	0.098	Positive	0.193	0.066	—	—	0.196
37. 52) 0.189)	0.135	Positive	0.215	0.10	—	—	0.161
38. 62) 0.226)	0.123	Positive	0.233	0.134	—	—	0.101
39. 50) 0.182)	0.113	Positive	0.171	0.067	—	—	—
40. 73) 0.266)	0.208	Positive	0.244	0.185	—	—	0.126
41. 46) 0.167)	0.073	Faintly positive	0.164	0.043	—	—	0.182
42. 53) 0.193)	0.112	Positive	0.226	0.065	—	—	0.182
43. 69) 0.251)	0.16	Positive	0.230	0.131	—	—	0.160
44. 87) 0.317)	0.215	Positive	0.318	0.169	—	—	0.204
45. 54) 0.197)	0.08	Faintly positive	0.198	0.043(?)	—	—	0.207
46. 105) 0.383)	0.302	Positive	0.365	0.300	—	—	—
47. 65) 0.237)	0.142	Positive	0.251	0.126	—	—	—
48. 25) 0.091)	Absent	Negative	0.058	—	—	—	—
49. 26) 0.094)	Absent	Negative	—	—	—	—	0.140
50. 28) 0.102)	Absent	Negative	—	—	—	—	0.137
51. 14) 0.051)	Absent	Negative	0.037	—	—	—	0.042
52. 59) 0.216)	0.08	Negative	0.208	—	—	—	0.179

NOTES.—30. Migraine. 31. Operation. Duodenal ulcer. 32, 33. ? Cirrhosis of liver.  
 34. Operation. Carcinoma of the body of the stomach. Inoperable. 35. Migraine. 36.  
 ? Appendicitis. 37. Operation. Duodenal ulcer. 38. Mucous colitis. 39. Operation.  
 Gastric ulcer. 40. Gastric ulcer. 41. Operation. Gastric ulcer. Hour-glass stomach. 42.  
 Enteroptosis. 43. Operation. Gastric ulcer (pylorus). 44. Duodenal ulcer. Operation for  
 ruptured duodenal ulcer 5 years ago. 45. Dyspepsia. 46. Operation. Duodenal ulcer.  
 47. Gastritis. 48. Post-mortem. Carcinoma of the stomach. 49. Persistent vomiting. ? Cause.  
 50. Chronic gastritis. 51. Gastritis. 52. Gastric ulcer. Haematemesis.

We believe that all the methods in the table (Table VII) have their inaccuracies. We will discuss each method separately:

1. *Töpfer's method*. This was originally described by Töpfer (*Zeitschr. f. Physiol. Chem.*, xix, Heft 1). Three equal parts of gastric contents are taken. All three are titrated with a decinormal solution of sodium hydrate. For the first phenolphthalein is used as an indicator, for the second alizarin, and for the third dimethylamidoazobenzene. Alizarin estimates all acidity except that due to protein-hydrochloric acid. We have not used this alizarin reaction owing to the difficulty of the end-point, and cannot discuss its meaning or accuracy.

*Phenolphthalein acidity*. This is generally considered to estimate free and combined hydrochloric acid, organic acids, and acid salts. The indicator gives the complete measure of acidity due to these substances. The result is recorded as 'Total Acidity'. We have found that filtered gastric contents have a slightly lower acidity than unfiltered, probably owing to the absorbing properties of the particles of bread. The result is more accurate with the filtered contents. The acidity is unaffected by standing even after many hours at room temperature. These remarks hold good equally for the dimethyl acidity. The end-point with phenolphthalein, and more particularly with dimethyl, is frequently indefinite in test-meals with low acidities.

*Dimethyl acidity*. This has been particularly investigated. In simple solutions free hydrochloric acid is estimated completely and accurately, and there is no reaction with protein-hydrochloric acid. We have confirmed this by numerous experiments on different forms of protein. For the estimation of free hydrochloric acid, the end-point is not reached until the solution becomes a light yellow colour. There is no reaction with acid phosphates even in strong solution. About one-third of the total acidity of lactic or acetic acid in simple solution is estimated. Exactly one-half of the acidity of free phosphoric acid is given. In a normal test-meal the dimethyl acidity is about two-thirds of the total acidity. In test-meals comparison of the dimethyl acidity with that calculated from the inversion of cane sugar shows a fairly close agreement when the acidity is high. When the acidity is low the dimethyl acidity is considerably above that estimated by the polariscope.

As a measure of free hydrochloric acid the dimethyl acidity is obviously inaccurate in some test-meals. For there may be a considerable acidity with a negative Günzberg reaction (see table). The dimethyl acidity in these cases is usually considered to be due to lactic, acetic, or butyric acid. We have found organic acids to account for only a very small portion of this acidity, since after prolonged extraction with ether the dimethyl acidity is little altered. In twenty-four hours, with several changes of ether, about 90 per cent. of the organic acids can be extracted from a watery solution. The almost negligible loss of acidity after ether extraction is shown in the table, and it is evident that the dimethyl acidity in these cases must be due to some other substance; we will discuss later the nature of this substance, which we believe to be in part phosphoric acid. The dimethyl acidity must therefore be considered in con-

junction with Günzberg's reaction. The indicator appears to give an accurate measure of free hydrochloric acidity when this is either normal or above normal. When the free acidity is below 0.1 per cent. the free hydrochloric acid is frequently over-estimated. The method has the great advantage of simplicity, and takes only a few minutes to perform. The total acidity with phenolphthalein can subsequently be estimated in the same specimen, and the Günzberg reaction performed at the same time. We thus obtain accurate information of the 'total acidity' and of the presence or absence of free hydrochloric acid, a reliable indication of an increase in this acid, and a less accurate estimation of a decrease. The entire examination takes about ten minutes to perform.

2. *Inversion of cane sugar.* The inversion of cane sugar is accelerated by the presence of free acids. For a given acid the amount of cane sugar inverted in a given time varies with the number of free ions present. Therefore, when the acid is sufficiently dilute to be completely dissociated, the amount of inversion will vary with the quantity of acid. The method has been shown to estimate free hydrochloric acid accurately, when in pure solution, in any strength in which it occurs in gastric contents. Hence by comparison with a solution containing a known quantity of hydrochloric acid, the amount of hydrochloric acid in gastric contents can be estimated.

The degree of dissociation of organic acids is so small that the amount of inversion due to their presence in gastric contents is negligible. Acid sodium phosphate and protein-hydrochloric acid have no effect on the rate of inversion. We found however that free phosphoric acid causes a definite acceleration. Therefore the method estimates the whole of free hydrochloric acid, part of free phosphoric acid, and practically no acidity due to organic acids. The technique described by Ham and McLeod has been followed in all cases.

We employed this method with the intention of controlling the dimethyl acidity as a measure of free hydrochloric acid. We shall show subsequently that when the total acidity is high and Günzberg's reaction is positive, phosphates are present in very small quantities. In these cases the method gives a very accurate estimation of the amount of free hydrochloric acid. Dimethyl acidity is also an accurate measure of free hydrochloric acid, since organic acids are present in very small amount. Indeed in such circumstances the same conclusions would almost invariably be drawn from the figures given by the dimethyl, Volhard's, and the polariscopic method.

When the total acidity is low, phosphates are present in greater quantity, especially when Günzberg's reaction is negative. The method then ceases to give an accurate estimation of free hydrochloric acid. As it measures phosphoric acid to a less degree than does dimethyl, and no organic acidity, it is somewhat more accurate than dimethyl, but the difference probably would never help in diagnosis. The filtrates are frequently so turbid that no estimation with the polariscope is possible. The acceleration of the inversion is thus an accurate measure of free hydrochloric acid when the acidity is high, but becomes inaccurate when the acidity is low. The method is of scientific interest but unpractical.

3. *Volhard's method.* The Volhard method employed was the modification described by Willcox, in which the difference between the total chlorides and the chlorides left after evaporating to dryness and heating over a Bunsen burner is reckoned as 'active' hydrochloric acid. Willcox, whose work on gastric analysis is of the highest value, does not concern himself with the free hydrochloric acid, but only with the 'active' or 'available' hydrochloric acid, i. e. the total of the free hydrochloric acid, and that combined with protein. We do not altogether agree with Willcox in theory, since by always giving the same simple test-meal after washing out the stomach the amount of available protein varies very little. Also, in the normal stomach, as the hydrochloric acid is neutralized by protein more hydrochloric acid is probably produced. In such a case the free and not the 'active' hydrochloric acid is the measure of the activity of the gastric functions. Moreover, the total available hydrochloric acid is not estimated, since a part of it is neutralized by salts in the test-meal, and is by this method ignored as 'fixed chlorides'.

In practice the 'active' hydrochloric acid agrees so closely with the total acidity that in the great majority of cases it gives no further information. This is evident on reference to Willcox's lists, particularly those relating to gastric ulcer, and to our own table. It can be said that if the total acidity is appreciably above or below normal, so is the 'active' hydrochloric acid, and slight variations between the two do not help us in any way. In Willcox's list of cases of gastric ulcer the total acidity and active hydrochloric acid agree to the third place of decimals. No case occurs in our table in which the total acidity is above normal and 'active' hydrochloric acid below normal, while all cases with very low acidity had very low active hydrochloric acid. We might point out that the estimation of total acidity takes ten minutes, and Willcox's method one and a half hours. The difference in labour is not compensated by the result.

Further we believe the method to be as inaccurate, and to vary from the facts in much the same way, as Töpfer's, i. e. it is probably fairly accurate when the result is high, and overestimates when low. We give the reasons shortly.

It is difficult at first sight to see a source of inaccuracy in the method. There is a possibility of loss of volatile chlorides during evaporation, but the amount of ammonium chloride is not great, and can only account for part of the difference between free and active hydrochloric acid, as Willcox has pointed out. In numerous mixtures of chlorides we found all the ammonium chloride lost by this method, but no loss of sodium chloride occurred even when the residue was heated to a red heat. Yet it seems to us the method must be inaccurate, since the active hydrochloric acid agrees fairly well with the total acidity whether Günzberg's reaction is positive or negative, and we are not inclined to accept Willcox's explanation of this, that in cases where Günzberg is negative the mucin is increased and the hydrochloric acid combines with it. The estimations of total nitrogen which we have performed do not show sufficient



variations in the amount of protein to account for the variations in the amount of protein-HCl as shown by Willcox's method.

We would call attention to the cases in Table VII in which Günzberg's reaction is negative and there is an appreciable dimethyl acidity. In such test-meals the dimethyl acidity must be deducted from the total acidity to obtain the extreme measure of the 'active' hydrochloric acid. Yet in some instances the 'active' hydrochloric acid is found actually to exceed the total acidity.

We would particularly call attention to Case No. 21, in which, with a negative Günzberg's reaction, the difference between the dimethyl and total acidity was 0.15 per cent. and the 'active' HCl was 0.22 per cent. In this case the dimethyl acidity of 0.10 per cent. was scarcely affected by extraction with ether, and was due, as we believe, to phosphoric acid. In these cases the 'active' hydrochloric acid must include something besides the hydrochloric acid combined with protein. We believe that the explanation is to be found in the mode of formation of the gastric hydrochloric acid, that is to say, by the interaction between sodium chloride and phosphoric acid.

In his article on Gastric Analysis in the previous number of this Journal, Dr. Graham lays much stress upon the ratio of active HCl to mineral salts of HCl. This ratio, just as the 'active HCl' upon which Willcox depends, seems to us to vary approximately with the total acidity. When, free HCl being present, the total acidity is high the active HCl is in excess of the mineral salts of HCl, the converse being the case when free HCl is absent and particularly when the total acidity is low. As a means of diagnosis this ratio in our opinion affords slightly less accurate information than the more simple method modified from Töpfer. Dr. Graham has found it convenient to provide separate tables for those cases of simple and malignant ulcer which do not conform to the rule. Several exceptions occurred among our cases, of which the most striking were a case of simple duodenal ulcer in which the ratio was 67 to 100, and a case of carcinoma of the stomach with a ratio of 317 to 100.

### *Phosphorus Compounds in Gastric Contents.*

So far as we have been able to ascertain, Moore is the only author in recent times who has directed attention to the interaction between phosphates and chlorides as a complication in the analysis of gastric juice. Moore carried out Günzberg's test on a decinormal solution of acid sodium phosphate to which he added successive tenths of its volume of decinormal hydrochloric acid. The test became positive with a mixture containing half as much hydrochloric acid as acid sodium phosphate. With mixtures containing less hydrochloric acid it was negative. It was noticed that with this mixture the pink colour denoting the presence of free mineral acid was not marked as with pure hydrochloric acid, but resembled the indefinite reactions which occur when examining the gastric juice of malignant cases. We have investigated further the results of

certain tests, qualitative and quantitative, when applied to solutions of phosphoric and hydrochloric acids and their sodium salts.

We will first consider the interaction of phosphates and chlorides in solutions. In a solution of chlorides and acid phosphates there will be present traces of disodium hydrogen phosphate and free hydrochloric acid. This is in accordance with Thomsen's law of Mass Action. If the amounts of the two salts are approximately equal, only a trace of hydrochloric acid will be present, in insufficient quantity to be recognized by such a test as dimethyl. If by any means this trace of hydrochloric acid can be removed, a further amount will be formed. It is generally supposed that hydrochloric acid in gastric juice is formed in this manner by the interaction of hydrogen sodium phosphate and sodium chloride in the gastric mucous membrane, the small amount of hydrochloric acid resulting being secreted into the cavity of the stomach. This action is continuous, and results in an appreciable amount of hydrochloric acid being present in the stomach. Removal of the hydrochloric acid by this vital action of the mucous membrane can be imitated by heating the solution of chlorides and acid phosphates over a water bath, the only volatile substance present being hydrochloric acid. By the time the solution has completely evaporated an appreciable quantity of chlorides will have been lost.<sup>1</sup> The following analysis may be quoted as an example:—

Solution—NaCl		.	.	.	.	.	0.5 gramme
NaH <sub>2</sub> PO <sub>4</sub>		.	.	.	.	.	0.2 gramme
Water to		.	.	.	.	.	100 c.c.
Analysis—Total Acidity		.	.	.	.	.	= 14
Free Acid		.	.	.	.	.	= 0
in 10 c.c.	{	Total Chlorides	.	.	.	.	= 8.4 c.c. $\frac{N}{10}$ AgNO <sub>3</sub>
		Chlorides after evaporation	.	.	.	.	= 7.8 „
		Chlorides lost	.	.	.	.	= 0.6 „

In this instance there is a loss of chlorides corresponding to 6 c.c. of decinormal silver nitrate solution in 100 c.c. This is equivalent to 0.022 gramme HCl. If a mixture of phosphoric acid and chlorides be taken the loss is much more marked.

Solution—NaCl		.	.	.	.	.	0.5 gramme
H <sub>3</sub> PO <sub>4</sub>		.	.	.	.	.	1 c.c.
Water to		.	.	.	.	.	100 c.c.
Analysis—Total Acidity		.	.	.	.	.	= 191
Free Acid		.	.	.	.	.	= 94
in 10 c.c.	{	Total Chlorides	.	.	.	.	= 8.2
		Chlorides after evaporation	.	.	.	.	= 0.1

Here the loss of chloride is the equivalent of 0.295 gramme HCl per cent.

<sup>1</sup> The results of these and of all subsequent analyses are recorded in the same form as for those of gastric juice. The phosphoric acid used was 'pure' phosphoric acid (sp. gr. 1.5) of the British Pharmacopoeia.

With organic acids the loss of chlorides is insignificant.

Solution—NaCl		0.5 gramme
Lactic Acid		1 c.c.
Water to		100 c.c.
Analysis—Total Acidity		= 85
Free Acid		= 34
in 10 c.c.	{ Total Chlorides	= 8.5
	{ Chlorides after evaporation	= 8.3

The addition of free HCl does not prevent the loss of chlorides.

Solution—NaCl		0.5 gramme
H <sub>3</sub> PO <sub>4</sub>		1 c.c.
$\frac{N}{10}$ HCl		50 c.c.
Water to		100 c.c.
Analysis—Total Acidity		= 239
Free Acid		= 141
in 10 c.c.	{ Total Chlorides	= 13.5
	{ Chlorides after evaporation	= 0.5

A mixture can thus be prepared the analysis of which closely approximates to that of gastric juice.

Solution—NaCl		0.5 gramme	Test-meal—	
H <sub>3</sub> PO <sub>4</sub>		0.25 c.c.	Case No. 43. Table VII.	
$\frac{N}{10}$ HCl		20 c.c.		
Water to		100 c.c.		
in 10 c.c.	Analysis—Total Acidity	= 69	Total Acidity	= 69
	Free Acid	= 42	Free Acid	= 44
	{ Total Chlorides	= 10.6	Total Chlorides	= 10.4
	{ Chlorides after		Chlorides after evaporation	= 4.1
	evaporation	= 4.9		
	Free Acid by		By polariscope	= 0.131%
	polariscope	= 0.147%		

Not only is the analysis of the above mixture almost identical with that of an actual test-meal, but it is also evident that the amount of chloride lost indicates a far greater amount of HCl than was in fact present in the solution. It is not suggested that ‘active’ hydrochloric acid is entirely due to the interaction of phosphates and chlorides, but these analyses are given to show the extent to which the presence of phosphates may influence its estimation.

We will next consider Günzberg’s reaction as applied to solutions containing phosphates. Solutions of pure phosphoric acid give a positive reaction even when very dilute. The presence of other substances interferes with this test.

Dextrose and Witte's peptone prevent phosphoric acid giving the reaction, and sodium chloride in a strong solution will also do so.

Peptone forms a compound with phosphoric acid as it does with hydrochloric acid, but its interference with Günzberg's test cannot be ascribed to this, as it may be negative when the presence of free acid is revealed by dimethyl. Dextrose does not diminish the acidity as estimated by either dimethyl or phenolphthalein, but Günzberg's test is negative after the addition of dextrose in certain quantities. Neither dextrose nor sodium chloride affect Günzberg's test when applied to free hydrochloric acid, and peptone only does so when in sufficient quantity to combine with the whole of the acid. Thus with these mixtures it is never found that Günzberg's test is negative when the dimethyl test is positive. This may be taken to prove that the action of these substances is not on the reagents used in the test. Considerable amount of sodium chloride is necessary to prevent free phosphoric acid from giving a positive Günzberg reaction.

With mixtures of sodium chloride and phosphoric acid a fleeting pink coloration is seen which agrees with Moore's observations referred to above, and is similar to what occurs in gastric juice with low acidity. The following example may be given of a solution in which Günzberg's test was negative, although free acid was undoubtedly present. The reaction also shows a loss in chloride of 0.08 gramme of HCl.

Solution—NaCl . . . . .		0.5 gramme
H <sub>3</sub> PO <sub>4</sub> . . . . .		0.25 c.c.
Witte's Peptone . . . . .		1 gramme
Water to . . . . .		100 c.c.
Analysis—Günzberg's Test . . . . .		=Negative
Total Acidity . . . . .		=62
Free Acid . . . . .		=21
in 10 c.c.	{ Total Chlorides . . . . .	= 8.4 c.c. $\frac{N}{10}$ AgNO <sub>3</sub>
	{ Chlorides after evaporation . . . . .	= 6.2 „
	{ Chlorides lost . . . . .	= 2.2 „

When estimating the acidity of solutions containing phosphates with phenolphthalein and dimethyl as indicators, the end-point is difficult to determine and differs from the sharp change which occurs with pure solutions of hydrochloric acid. With dimethyl there is a long range of orange tints between the disappearance of the pink and the appearance of the light yellow which marks the completion of the titration. With phenolphthalein conversely there is a long interval between the first appearance of a reddish tint and the definite establishment of the pink colour which is distinctive of alkalis in pure solution. Thus a considerable error easily arises in estimating such acidities. The polariscope is of little assistance. Inversion of cane sugar is appreciably accelerated by phosphoric acid, but it is difficult to decide the exact point at which there is a uniform purple colour. Thus there may be definite errors in the estimation of

the angle of rotation. Solutions to which protein has been added are even more difficult, as they have considerable opacity.

All these indefinite end-points are present in gastric juice in which the acidity is low, and especially in cases when free hydrochloric acid is absent. In such cases the filtrate is frequently so cloudy that no light penetrates the polariscope; when sufficiently diluted to be translucent, the change in the angle of rotation becomes so small that the estimation is unreliable. Hence the polariscope entirely fails us in cases in which the error of other methods is greatest.

These reactions show the resemblance between the solutions containing phosphates and gastric juice of low acidity. We have already given our reasons for believing that the estimation of the active hydrochloric acid is especially erroneous in these cases. The test-meal may be referred to again in which the 'active' hydrochloric acid was 0.22 per cent. while the difference between the dimethyl and total acidity corresponded to 0.15 per cent., free HCl being absent. The 'active' hydrochloric acid must therefore have been over-estimated by at least one-third, even supposing the whole of the 0.15 per cent. to comprise hydrochloric acid combined with proteid.

We will next consider the amount of phosphates present in gastric juice from various conditions. The estimation of the phosphates in test-meals by the use of uranium nitrate was found to be unsatisfactory. It is recognized that the presence of chlorides, especially hydrochloric acid, interferes with the reaction. An attempt was made to estimate the amount of acid sodium phosphate by titrating the remaining acidity with decinormal soda. This method is based on the incorrect assumption that acid sodium phosphate is not neutralized by calcium carbonate. With pure solutions of phosphoric acid an approximate result can be obtained by titrating immediately after the addition of calcium carbonate. Acid sodium phosphate, however, is neutralized by calcium carbonate almost completely in about an hour.

It is impossible to obtain any measure of the amount of acid sodium phosphate in a test-meal by titrating immediately after the addition of calcium carbonate, since protein-hydrochloric acid is found to be neutralized by calcium carbonate even more slowly than is acid sodium phosphate. The following method was finally used in the estimation of phosphates:—Evaporate 20–40 c.c. of filtered gastric contents to dryness or a water bath. Add about 40 c.c. of strong nitric acid and stir. The solution will have a yellow colour. Heat again on the water bath, and add small quantities of potassium chlorate until the solution becomes clear. This destroys all organic matter. Evaporate to dryness on the water bath. All the chlorides present will have passed off as nitrosyl chloride. The residue will be of a syrupy consistency. Add to this 50 c.c. of a solution of ammonium molybdate in nitric acid. The whole of the phosphoric acid is precipitated on heating. The precipitate, which is filtered off, has approximately the formula  $10\text{MoO}_3\cdot\text{PO}_4(\text{NH}_4)_3$ . As the precipitate is soluble in water it must be washed with the reagent. The filter paper is then dried at

a moderate heat, but must not be ignited. The precipitate can then be brushed off the dry paper, and weighed directly. The amount of phosphates present is calculated from the formula of the precipitate.<sup>2</sup>

The accompanying table (Table VIII) gives the analyses of test-meals, chosen indiscriminately.

It will be noticed that the amount of phosphate is greatest when free hydrochloric acid is shown to be absent by Günzberg's test, and the total acidity is relatively high. This is probably not due to a simple failure on the part of the stomach to absorb the phosphates taken in the food, but is more likely to depend upon the method of formation of hydrochloric acid referred to above. It is possible that an abnormal gastric mucous membrane, failing to evolve hydrochloric acid from the mixture of phosphates and chlorides brought to it from the blood, secretes the phosphates into the stomach unaltered.

We are unable for various reasons to agree with the view that the absence of free acid in carcinoma is due to a neutralization by an alkaline secretion from the ulcer. If this were the case there should be no diminution of the total chlorides in carcinoma cases, whereas there is a marked decrease, such as does not occur if an alkali be given with the test-meal to a normal individual.

In those cases in which the total acidity is approximately normal and the Günzberg test is negative, the acidity is partly due to the phosphates, since in an acid medium these can only exist as acid salts. The amount present is sufficient to cause a considerable loss of chloride on heating to dryness, and this is indistinguishable from protein-hydrochloric acid; we perform indeed by means

TABLE VIII.

No. of Case.	Total Acidity.	Dimethyl Acidity.	Günzberg's Reaction.	Phosphates (grammes %).
1	49	0.066	Negative	0.11
2	40	Absent	Negative	0.082
3	30	Absent	Negative	0.075
4	48	0.055	Negative	0.056
5	45	0.07	Negative	0.05
6	34	Absent	Negative	0.05
7	54	0.10	Positive	0.042
8	34	0.03	Negative	0.04
9	34	0.04	Negative	0.038
10	45	0.055	Trace	0.036
11	41	0.07	Positive	0.031
12	77	0.18	Positive	0.025
13	53	0.095	Positive	0.022
14	58	0.14	Positive	0.012
15	14	Absent	Negative	0.010
16	61	0.12	Positive	0.006
17	60	0.12	Positive	0.003

of an evaporating dish and a Bunsen burner exactly what the gastric mucous membrane has failed to do. Thus in such cases the amount of phosphates is sufficient to cause considerable inaccuracy in the estimation of 'active' hydro-

<sup>2</sup> v. *Dictionary of Chemistry*, part VIII, 3rd supplement, 'Phosphates.'

chloric acid. In cases where the free acidity is normal, or above normal, phosphates become of minor importance.<sup>3</sup>

It is possible, but improbable, that the amount of phosphates present may help us in the diagnosis of carcinoma of the stomach; so far as our investigations have gone the amount of phosphate varies with the presence or absence of free HCl, irrespective of the kind of lesion present in the mucous membrane.

### *The Amount of Protein in Gastric Contents.*

The amount of nitrogen in filtered gastric contents has been estimated in seventeen cases by Kjeldahl's method. Some idea of the amount of hydrochloric acid combined with protein can be obtained from the figures. The term 'protein-hydrochloric acid' is applied commonly to the difference between the 'active hydrochloric acid', as estimated by Volhard's or other methods, and the free hydrochloric acid. This theoretically gives the amount of hydrochloric acid combined with protein.

Since dimethyl certainly estimates the whole of the free hydrochloric acid the 'protein-hydrochloric acid' must be at least equal to the difference between the 'active' and the dimethyl acidity. Any other method of calculation will make the result greater. One gramme of a sample of Witte's peptone was found by titration to combine with 0.035 gramme of hydrochloric acid. It contained 0.162 gramme of nitrogen.

In the accompanying table (Table IX) twelve cases are given in which the 'active' and dimethyl acidity have been estimated, and the total nitrogen.

It will be seen that the amount of 'protein-hydrochloric acid' calculated as above is far greater than corresponds to the amount of nitrogen, according to

TABLE IX.

No. of Case.	Active HCl.	Dimethyl Acidity.	Difference (=Protein-HCl).	Total Nitrogen.
10	0.156	0.04	0.116	0.140
36	0.193	0.098	0.095	0.196
37	0.215	0.135	0.080	0.161
38	0.233	0.123	0.110	0.101
40	0.244	0.208	0.036	0.126
41	0.164	0.073	0.091	0.182
42	0.226	0.112	0.114	0.182
43	0.230	0.16	0.070	0.160
44	0.318	0.215	0.103	0.204
45	0.198	0.08	0.118	0.207
51	0.037	Absent	0.037	0.042
52	0.208	0.08	0.128	0.179

the results obtained with Witte's peptone. The various degradation products of protein have been shown by Cohnheim to combine with varying amounts of

<sup>3</sup> An estimation of the phosphates present in the filtrate of a mixture of tea and toast differed little from that found in gastric contents withdrawn from a normal person.

hydrochloric acid, and hence the results obtained with Witte's peptone cannot be regarded as more than a rough guide, but the difference between the theoretical amount of 'protein-hydrochloric acid' and that found by these methods is excessive.

The analysis of a solution containing Witte's peptone is given as an illustration of what may occur with gastric contents:—

Solution—Phosphoric Acid . . . . .	0.25 c.c.
NaCl . . . . .	0.5 gramme
Witte's Peptone . . . . .	1 gramme
Water to . . . . .	100 c.c.
Analysis—Günzberg's Reaction . . . . .	= Negative
Total Acidity . . . . .	= 62
Free Acid . . . . .	= 21 (0.077 %)
Total Chlorides . . . . .	= 8.4
Chlorides after evaporation . . . . .	= 6.2

The 'active hydrochloric acid,' thus amounts to 0.08 per cent. As Günzberg's reaction is negative, the solution cannot contain any appreciable amount of free hydrochloric acid. Hence in gastric contents all the 'active hydrochloric acid' would be regarded as combined with protein. In this solution we know that there cannot be more than 0.035 per cent. of protein-hydrochloric acid. The analysis is explained by the loss of 0.045 per cent. of acid through the interaction of phosphates and chlorides.

In two cases the nitrogen has been estimated in gastric contents in which Günzberg's reaction was negative. The quantity is not above the average, and the result does not support the view that absence of free hydrochloric acid is due to an excessive amount of protein combining with the hydrochloric acid. The amount of nitrogen does not vary greatly, except in two instances in which it was distinctly above the average. In both of these the acidity was also high.

### *Conclusions.*

1. The analyses of gastric contents by methods commonly in vogue show that all these methods are approximately accurate when the free acidity is either normal or above normal, and inaccurate when the free acidity is low.

2. We agree with Dr. Willcox in considering the Prout-Winter method to be inaccurate in any circumstances.

3. We do not agree that the estimation of 'active' (Willcox) hydrochloric acid is either accurate or profitable. This conclusion is based on the following:—

(i) That no further information is obtained from the active hydrochloric acid than from the total acidity estimated by phenolphthalein.

(ii) When the free acidity is low or absent the active hydrochloric acid is



over-estimated owing to the interaction of fixed chlorides with phosphorous compounds, the phosphates being increased in these conditions.

(iii) We find no increase of the total nitrogen in cases in which free hydrochloric acid is absent, whilst the active 'hydrochloric acid' is normal.

4. Phosphates introduce a fallacy common to all the methods which we have investigated. The analyses show the following points:—

(i) The amount of phosphates is very small in gastric contents with a high acidity and a positive Günzberg's reaction.

(ii) The amount of phosphates is largest in gastric contents in which Günzberg's reaction is negative but the acidity high.

(iii) The amount of phosphates varies roughly with the acidity between these two extremes.

(iv) The interaction of phosphates and fixed chlorides results in a loss of chlorine when the solution is heated and dried.

(v) The amount of phosphates present in cases with a low acidity is probably independent of the clinical condition; thus it does not assist in differentiating a case of gastritis from one of carcinoma of the stomach.

5. We suggest that the phosphates are secreted into the cavity of the the stomach when the gastric mucous membrane fails to elaborate free hydrochloric acid from the mixture of phosphates and chlorides brought to it from the blood.

6. We have arrived at the conclusion that the simple method used in the first part of this investigation (viz. Günzberg's reaction and the estimation of total and diastyl acidity) is as accurate as more elaborate methods, and supplies to the clinician all the assistance and information which can reliably be obtained from the chemical examination of gastric contents.

We are indebted to the members of the Staff of the London Hospital for permission to make use of their cases, and we have to thank Dr. Robert Hutchison for his suggestions regarding the effect of hæmorrhage on the gastric secretions.

# THE SYSTOLIC PRESSURE AT DIFFERENT POINTS OF THE CIRCULATION IN THE CHILD AND THE ADULT<sup>1</sup>

By LEONARD FINDLAY

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THE question of the distribution of the pressure in the more central and peripheral arteries was first studied by Hürthle (8), who found at different points of the arterial tree very different readings for the systolic pressure. According to Janeway (3), however, the lateral pressure in the small arteries, if not of too small diameter, has been proved by all recent investigation to diminish extremely slowly with the increasing distance from the heart, and the first appreciable fall takes place in the capillaries.

Although this latter opinion seems to be correct where more or less perfectly elastic arteries are concerned, when the walls of the smaller arteries, either from disease or as the result of muscular contraction, are less elastic the difference between the central and peripheral pressures becomes very marked.

For the estimation of arterial pressure in the more central arteries various modifications of the Riva-Rocci apparatus are used, while for the measurement of the pressure in the arterioles the Gärtner's tonometer may be employed. Since the conditions of the arterioles vary so considerably it is only natural to expect that the results of the tonometer observations should vary somewhat. It is probably on this account that the Gärtner tonometer has never enjoyed a great popularity, and is not so suitable for ordinary clinical investigations as the modifications of the Riva-Rocci instrument.

Hayaski (2) investigated the blood-pressure with both the Riva-Rocci and Gärtner's instruments in 58 adults and 108 children, and found that, irrespective of age or sex, the latter gave the lower readings. The difference between them was 21 mm. in the child and adult male, and 22 mm. in the case of women. Von Recklinghausen (6), in contrast to Hayaski, obtained readings higher to the extent of 7 mm. in the fingers than in the brachial artery. Müller and Blauel (5) in one case compared the results obtained with Gärtner's tonometer and the kymograph. The estimations were carried out on a limb about to be amputated, canulae being inserted into the brachial and radial arteries and

<sup>1</sup> In aid of the above research a grant was obtained from the Carnegie Trust.

the pressure directly measured, while simultaneous readings with Gärtner's instrument were taken. Their results (systolic pressure) were as follows:—

Brachial Artery.		Gärtner.	
Feather manometer	109	Left middle finger	110-115
Mercury manometer	94	" " "	100-105
Radial Artery.		Gärtner.	
Feather manometer	115	Left ring finger	120-126
Mercury manometer	106	" " "	120-126

Here a higher estimation was obtained at the digital artery than in either the brachial or radial arteries. This higher reading is probably to be accounted for by the fact that all sphygmomanometers give abnormally high estimations, as a certain amount of pressure is required to overcome the resistance of the arterial wall. This is a point about which there has been within recent years much discussion, Janeway and Hill holding that the arterial wall is a negligible quantity, while Russell on the other hand holds that it is the most important factor in arterial pressure as gauged by clinical methods. Müller and Blauel's work with the kymograph, and the Gärtner and Riva-Rocci instruments as well, lends support to the latter view.

The observations which I am about to detail have been made on healthy and sick individuals of both sexes, and of ages varying between two and a half and fifty years. I have classed the cases into age periods of ten years each, and in the cases between twenty and thirty years the sexes have been separately considered.

The Riva-Rocci instrument which I employed was an American model, and was provided with an armlet four inches broad. In using the tonometer I placed the ring, as advised by Gärtner himself, on the middle phalanx of either the middle or ring finger, and used, as the sign of systolic pressure, not the first change in colour of the nail, but the sudden and general flushing of the same. This was a very definite phenomenon, and in the older patients was usually found to coincide with the appearance of a feeling of pulsation in the tip of the finger.

TABLE I.  
Age from 2½ years till 10 years.

No.	Age.	Brach. Sys. Press.	Digit. Sys. Press.	Difference.
1	2½ years	65	70	+ 5
2	2¾ "	70	50	- 20
3	3 "	60	80	+ 20
4	3 "	80	80	0
5	4 "	75	75	0
6	4 "	75	75	0
7	4 "	102	95	- 7
8	4 "	98	100	+ 2
9	4 "	85	85	0
10	4 "	65	65	0
11	4 "	70	75	+ 5
12	5 "	75	75	0
13	5 "	90	80	- 10
14	5 "	75	75	0
15	5 "	70	70	0

TABLE I (*continued*).

No.	Age.	Brach. Sys. Press.	Digit. Sys. Press.	Difference.
16	5 $\frac{8}{12}$ years	72	68	- 4
17	6 " "	75	70	-10
18	6 $\frac{1}{2}$ " "	90	95	+ 5
19	7 " "	85	80	- 5
20	7 $\frac{1}{2}$ " "	98	85	-13
21	8 " "	95	95	0
22	8 $\frac{1}{2}$ " "	92	90	- 2
23	8 $\frac{1}{2}$ " "	95	90	- 5
24	9 " "	85	80	- 5
25	9 " "	80	75	- 5
26	9 " "	90	85	- 5
27	10 " "	95	90	- 5
28	10 " "	85	80	- 5
29	10 " "	85	85	0
30	10 " "	125	125	0

Average difference = 4.6 mm.

TABLE II.

Including cases between 10 and 20 years.

No.	Age.	Brach. Sys. Press.	Digit. Sys. Press.	Difference.
1	10 $\frac{1}{2}$ years	98	95	- 3
2	10 $\frac{1}{2}$ " "	85	83	- 2
3	10 $\frac{1}{2}$ " "	95	95	0
4	10 $\frac{1}{2}$ " "	95	95	0
5	11 " "	95	100	+ 5
6	11 " "	100	90	-10
7	11 " "	70	70	0
8	12 " "	80	70	-10
9	12 " "	95	90	- 5
10	12 " "	135	100	-35
11	14 " "	90	85	- 5
12	14 " "	93	70	-23
13	14 " "	80	75	- 5
14	14 " "	85	80	- 5
15	15 " "	85	85	0
16	15 " "	100	70	-30
17	19 " "	120	120	0
18	19 " "	110	105	- 5

Average difference = 8 mm.

TABLE III.

Including cases between 20 and 30 years.

## A. Males.

No.	Age.	Brach. Sys. Press.	Digit. Sys. Press.	Difference.
1	21 years	100	70	-30
2	23 " "	110	80	-30
3	25 " "	110	80	-30
4	26 " "	115	100	-15
5	26 " "	105	100	- 5
6	26 " "	115	70	-45
7	26 " "	112	90	-22
8	21 " "	140	120	-20

Average difference = 22.1 mm.

TABLE III (*continued*).B. *Females.*

No.	Age.	Brach. Sys. Press.	Digit. Sys. Press.	Difference.
1	21 years	105	100	- 5
2	22 "	125	100	-25
3	30 "	125	115	-10
4	30 "	140	135	- 5
5	30 "	125	110	-15

Average difference = 13 mm.

TABLE IV.

Including males between 30 and 40 years.

No.	Age.	Brach. Sys. Press.	Digit. Sys. Press.	Difference.
1	31 years	102	80	-22
2	31 "	110	100	-10
3	31 "	100	70	-30
4	31 "	100	70	-30
5	31 "	155	100	-55
6	35 "	110	90	-20
7	35 "	105	85	-20
8	35 "	115	80	-35
9	37 "	125	80	-45
10	38 "	113	70	-43
11	38 "	100	50	-50

Average difference = 32 mm.

TABLE V.

Including males between 40 and 50 years.

No.	Age.	Brach. Sys. Press.	Digit. Sys. Press.	Difference.
1	42 years	158	70	-88
2	43 "	115	75	-40
3	43 "	165	110	-55
4	45 "	110	50	-70
5	45 "	145	65	-80
6	45 "	110	70	-40
7	45 "	110	70	-40
8	47 "	110	90	-20
9	47 "	100	90	-10
10	48 "	142	140 ?	- 2

Average difference = 44.5 mm.

A most striking feature in these tables is the gradually increasing difference between the so-called central, or brachial pressure, and the peripheral, or digital pressure. During the first decade the average difference amounts to 4.6 mm. of mercury. In the majority of the cases the brachial reading is higher than the digital, though in 20 per cent. the opposite is found. Between ten and twenty years this difference rises to 8 mm., and in only 5 per cent. of the cases is a higher peripheral reading obtained. From twenty to thirty years the difference is still higher, registering for men 22.1 mm. and for women 13 mm., and in every case the brachial blood-pressure recorded the higher register. In the case of men between thirty and forty years the average difference is 32 mm., and for men between forty and fifty years 44.5 mm.

It is thus seen that the older the individual and the higher the blood-pressure, the greater is the difference between the central and peripheral readings. This state of matters under the latter condition is well borne out in the cases which have an abnormally high blood-pressure for their age, the difference in these instances exceeding the average.

TABLE VI.

No.	Age.	Disease.	Brach. Sys. Press.	Digit. Sys. Press.	Differ- ence.	Average.	Normal differ- ence for this age period.
1	4 years	Acute Bright's	102	95	7	8.5	4.6
2	10 "	Bronchitis	110	100	10		
3	12 "	Nephritis	135	110	25	25	8.0
4	22 " (f.)	Nephritis	195	130	65	65	13.0
5	32 "	Nephritis	190	120	70	85	32.0
6	35 "	Nephritis	180	80	100		
7	42 "	Double Aortic	158	70	88	73	44.5
8	43 "	Acute Bright's	165	110	55		
9	43 "	Acute Bright's	185	130	55		
10	44 "	Acute Bright's	185	90	95		

Moreover, in acute Bright's disease, where estimations were made before and after the fall in the blood-pressure, the same point is observed, viz. the higher the pressure the greater the difference between the central and peripheral readings.

TABLE VII.

(a) J. M. (female), acute Bright's disease.

	Brach.	Digit.	Difference.
23/1/09	195	130	65
30/1/09	125	110	15

(b) J. R., aged 35 years (male), acute Bright's disease.

	Brach.	Digit.	Difference.
23/11/08	180	80	100
8/12/08	115	80	35

(c) A. P., aged 26 years (male), acute Bright's disease.

	Brach.	Digit.	Difference.
17/1/11	145	105	40
21/1/11	95	70	25

How can we explain this phenomenon? To my mind the cases of high blood-pressure in acute Bright's disease give us a clue to the explanation. In the condition of high blood-pressure there is an increased tonus of the arterial wall, which acts in a 'stop-cock' fashion, cutting off to a certain extent the pressure wave. By the use of arterio-constrictors, in man and animals, I have been able to induce this increased arterial tonus experimentally, and have obtained results which lend considerable support to this view.

In the experiments on animals, cats being used, I employed intravenous injections of adrenalin, and estimated simultaneously the pressure in the carotid artery by means of the kymograph, and in the smaller arteries of the paw by Gärtner's tonometer. The following are the results obtained:—

Experiment I.	Carotid.	Paw.	Difference.
Before drug . . . . .	110	60	50
After adrenalin, 1st dose . . . . .	170	55	115
„ „ 2nd dose . . . . .	190	50	140

Experiment II.	Carotid.	Paw.	Difference.
Before drug . . . . .	80	30	50
After adrenalin . . . . .	140	45	95

Experiment III. (In this case both vagi were cut in order to avoid cardiac inhibition.)

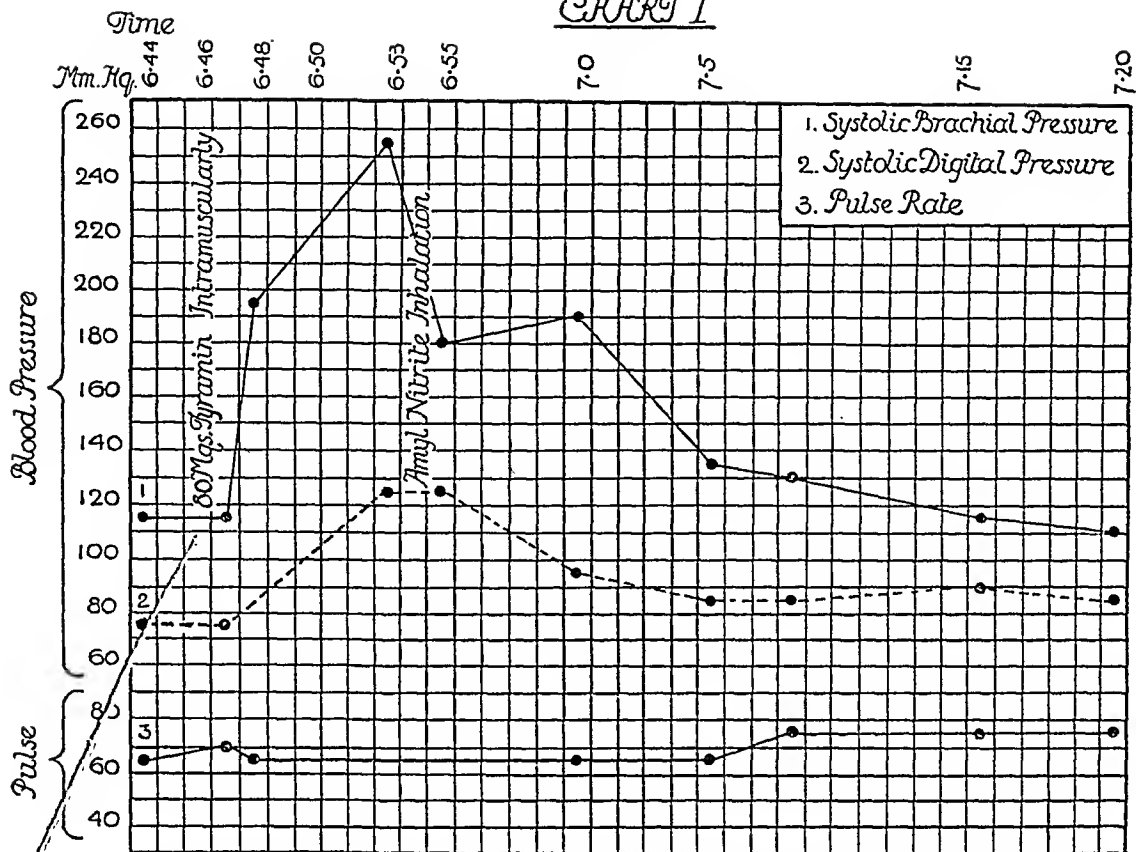
	Carotid.	Paw.	Difference.
Before drug . . . . .	146	80	66
„ „ . . . . .	164	150	14 ?
After adrenalin, 1st dose . . . . .	200	150	50
„ „ 2nd dose . . . . .	164	50	114

The last experiment is not so convincing as the other two, but nevertheless they all demonstrate the same point—that the constricted arteries cut off the pressure wave, so that by the use of such drugs (arterio-constrictors) it is impossible to raise the peripheral pressure equally with the central.

So far as the human subject is concerned I experienced great difficulty in obtaining a substance which, without being injected intravenously, would raise the blood-pressure. Ultimately I found a satisfactory drug for this purpose in Dale's synthetic preparation called 'Tyramin' (1) (parahydroxyphenylamine), manufactured by Burroughs, Wellcome & Co. Intramuscular injections of this drug in doses of from 20 to 80 mgs. caused a sudden and marked rise in the blood-pressure. The effect was noticed within five minutes, reached its maximum within ten minutes, and in all my subjects had entirely disappeared within twenty minutes, but as a rule the effect passed off within fifteen minutes. Sometimes, and especially when large doses were given, there was a secondary fall in the pressure. The cardiac pulsations were slowed and greatly increased in force. The larger doses were, unfortunately, accompanied by excruciating headache, of which I can speak from experience, and which persisted for some time after the return of the pressure to normal. It was thus almost certain that in the cerebral arteries there was also a considerable rise in the pressure—a point which would make me very careful of its use in adults, as to my mind the risk of cerebral haemorrhage must be considerable. It was also found that the higher the blood-pressure the greater was the difference between that registered at the brachial and at the digital arteries. The two following charts may be taken as typical of the effects of a moderate and of a large dose of tyramin.

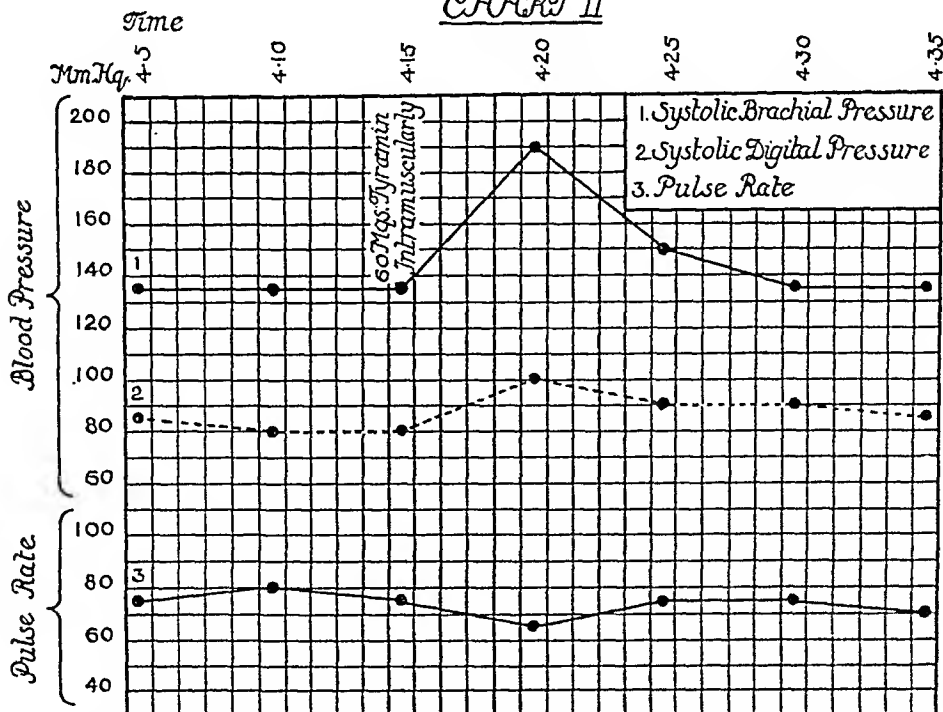
As further supporting the idea that the increased rigidity or tonus of the arterial wall is the cause of the gradual fall in blood-pressure, the behaviour of

## CHART I



L.F. aet. 33 years. Within three minutes felt throbbing in chest and soon afterwards pain in head which became so intense that Amyl Nitrite had to be administered

## CHART II



A.W. aet. 21 years. Only sensation felt was beating of heart and in vessels of neck. No headache.



the pressure wave as it passes along tubes of varying consistency may be cited. It is known that the lateral pressure of fluid in a tube with a free outlet behaves differently according to the type of material of which it is composed. In a rigid tube there is a steady and gradual decline in the pressure as the outlet is approached (Fig. 1), while in an elastic tube the pressure at first suddenly falls, and then either preserves a steady level or only very gradually continues to descend (Fig. 2). This latter curve is drawn to scale from the experimental tracings of Marey showing the rate of passage of the pulse wave along an elastic tube, which are reproduced by McKendrick (4). The amplitude of the pulsations has been taken as the measure of the lateral pressure.

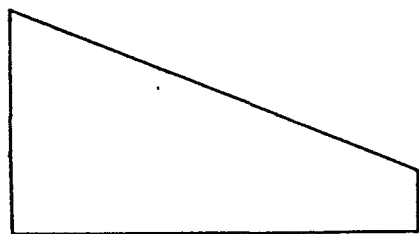


Fig 1

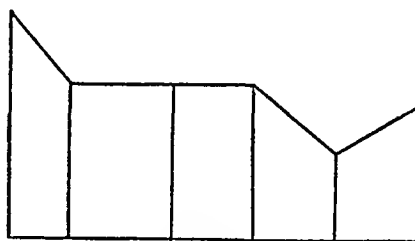


Fig 2

As the systolic pressure in the brachial artery is lower than what obtains in the first part of the aorta, it is not unlikely that in the case of children with elastic arteries there is a sudden and great fall in the pressure before the brachial artery is reached; and from there onwards, at least as far as the digital arteries, the same level is preserved. In the adult, whose arteries are more or less sclerosed, or in acute Bright's disease, where the arteries are tonically contracted, the elasticity of the vessel is diminished and more nearly approaches the character of a rigid tube. In these cases there will be a steady decline in the blood-pressure from the centre to the periphery.

However we may explain the condition the fact remains that the transmission of the pressure wave from centre to periphery behaves differently in the child and in the adult. In childhood and youth, and for a longer period in women than in men, the systolic pressure at the digital artery equals that registered at the brachial artery. In the adult, on the other hand, and in diseases accompanied by high blood-pressure (arterio-sclerosis and Bright's disease), the systolic brachial pressure is much higher than the systolic digital pressure.

In conclusion I must acknowledge my thanks to Prof. D. Noël Paton, at whose instigation this work was commenced, and in whose laboratory some of the experiments were carried out.

### *Conclusions.*

1. During childhood and youth the systolic arterial pressure is fairly uniform at different points of the circulation.
2. In adult life the peripheral systolic pressure is lower than the central, and the difference between them increases with age.

3. The difference greater than normal between the central and peripheral systolic pressures in cases of hyper-tension—from disease or experimentally induced—supports the idea that the behaviour of the pressure and its variations depends upon changes in the elasticity of the vessel wall.

## BIBLIOGRAPHY.

1. Dale and Dixon, *Journ. Physiol.*, Camb. and Lond., 1909-10, xxxix. 25.
2. Hayaski, *Inaug. Dissert.*, Erlangen, 1901 (quoted by Janeway, *Clinical Study of Blood Pressure*, New York, 1904, 130).
3. Janeway, *Clinical Study of Blood Pressure*, New York, 1904, 30.
4. McKendrick, *Outlines of Physiology*, Glasgow, 1878, 339.
5. Müller and Blauel, *Deutsch. Archiv f. klin. Med.*, 1907, xci. 517.
6. von Recklinghausen, *Archiv f. exp. Path. und Pharm.*, Leipz., 1901, xlv. 78.
7. Schäfer, *Text Book of Physiology*, Edinb. and Lond., 1900, ii. 63.
8. Schäfer, *ibid.*, 81.

# CONTRIBUTION TO THE STUDY OF THE FUNCTION OF THE A-V BUNDLE

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With Plates 41-46

BOTH experiment and clinical experience have shown the importance of the  $\alpha$ -v bundle in conveying the stimulus from auricle to ventricle, and numerous experiences from pathology illustrate how the co-operation between these two parts of the heart may be disturbed by pathological changes in the said bundle. However, it has not yet been fully demonstrated to what extent the  $\alpha$ -v bundle is the only way by which the functional connexion between auricle and ventricle may be established. Certain phenomena appear to indicate that a regular co-agency between auricle and ventricle can perhaps be established, at least for some time, even if the bundle is put out of action. On the other hand, neither is it fully demonstrated to what extent and in what manner this co-operation between auricle and ventricle can be diminished or destroyed by certain conditions outside the  $\alpha$ -v bundle itself. In both these respects, the cases which are to be discussed below may perhaps contribute towards extending our knowledge to some degree.

## Case No. I.

*Adams-Stokes syndrome with chronic bradycardia for many months, interrupted by short paroxysms of tachycardia. The post-mortem microscopical examination of the heart shows a destruction completely across the chief trunk of the  $\alpha$ -v bundle.*

The patient was 72 years of age, and lay in the University Hospital, Christiania ('Rikshospitalet'), from Sept. 18, 1906, until his death, July 27, 1907. He was quite well until shortly before his admission to the hospital, when he began to suffer from fainting fits. In the hospital it was found that he suffered from mitral regurgitation, with some hypertrophy of the heart, some arterio-sclerosis, and a slight effusion into the left pleura. There was also a trace of albumin in the urine. The pulse, which was full and of high tension (the arterial systolic tension 195 mm. by Riva Rocci's manometer), was not always regular, extra-systoles appearing now and then. These extra-systoles were without compensatory pause, as is to be found when extra-systoles appear in a ventricle working automatically, as is pointed out by Wenekebach (7). Such extra-systoles appeared on the whole but seldom; as a rule the pulse was regular, or evinced now and then irregularities which could not be declared as extra-systolic. It was only immediately after the paroxysms, which will be described later, that extra-systoles appeared constantly and in greater numbers. Between the attacks the speed of the pulse was generally 20-30 per minute. Exertion did not increase the rate of the pulse, nor did a subcutaneous injection of 1 mg. atropine.

At the apex two sounds were heard, the first soft blowing.

The veins of the neck were somewhat swollen. For every beat at the apex two or three pulsations in the veins of the neck could be counted, and on the Röntgen screen it could be clearly seen that the auricle contracted at a much greater speed than the ventricle: 60-70 auricle contractions per 20-30 ventricle contractions could clearly be counted. Among the numerous tracings taken between the attacks, Fig. 1 shows clearly a complete heart-block and Fig. 2 shows the same with tracing from the liver above and radial below; Fig. 3 shows a long radial intermission without loss of consciousness, with indications of anacrotism in the first pulsations after the intermission.

*The attacks.* The patient, in addition to a number of slight attacks of giddiness, had four more serious attacks, with loss of consciousness and sometimes indications of convulsions.

The first of these attacks occurred in the evening of Jan. 24, 1907, when the patient suddenly fell unconscious on the floor. The house physician, who arrived almost immediately after, described his condition as follows:—

The patient was cyanotic; after a few deep respirations breathing entirely stopped. The apnoea lasted a rather long time.

The pulse and heart's action during the seizure were easy to count, both 140 per minute, quite regular. After the apnoea had lasted a while he woke up at once to full consciousness. After the attack the frequency of the pulse sank rapidly. Ten minutes after the commencement of the attack it was 120, fifteen minutes after it was 60, and three-quarters of an hour after it was 35. During the night the patient had four more slight, quite brief attacks of fainting and a short fit of shivering.

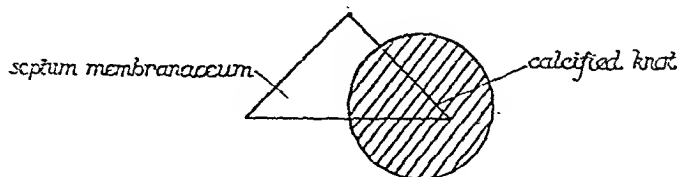
The day after the attack he was slightly confused, but was otherwise in his normal condition. He had no recollection of what had taken place. On May 22, July 3, and July 26 the patient had an attack that in all essentials resembled the one described. By the second one unconsciousness lasted several minutes; the frequency of the pulse during the attack was 156, the pulse was regular and equal; ten minutes after the commencement of the attack the frequency had gone down to 56. The last attack (July 26) was the most severe. The house physician, who arrived five minutes after the attack, found the patient unconscious, strongly cyanotic, perspiring, in complete apnoea; the pulse could not be felt, no movement of the veins of the neck could be perceived, the muscles of the abdomen were greatly contracted. After artificial respiration had been applied the patient began to respire, at first stertorously, irregularly, whilst the respirations were now and then interrupted by hiccupping. Just after the respiration commenced again the pulse was 160, regular; forty minutes later it was 56. It was only after about one and a half hours that the patient came to full consciousness. The urine passed after the attack contained albumin, but no sugar. (The urine was by chance also examined immediately before the attack. It was then free from albumin.) The patient died the next night quite suddenly, probably under an attack. The post-mortem examination (Professor Harbitz) showed briefly the following:—

The heart was enlarged throughout (weight 590 grm.). The mitral valve calcified and the mitral ostium somewhat contracted. The calcareous infiltrations were continued into the septum membranaceum; on the right side this calcification could be seen (cf. Fig. 4) as a projecting knot, the size of a pea and calcified right through, occupying the front part of the septum membranaceum.

Also the aortic valves, especially the left, were calcified so that the calcareous encrustations from the mitral valve and septum membranaceum were continued directly to the aortic valves.

Both of the coronaries were calcified, but in no place obliterated or contracted. Macroscopically the muscles of the heart appeared normal, excepting certain small fibrous scars in the left ventricle. The macroscopic appearance of the calcareous knot and its situation alone made it highly probable that the

main trunk of the *a-v* bundle must be damaged by the calcareous masses to a greater or lesser extent. The microscopic examination also showed that the main trunk of the *a-v* bundle had disappeared entirely, leaving not a trace of its normal tissue in the great calcareous knot. (Cf. Fig. 5, *a*, *b*, *c*, *d*.)



The microscopic examination was carried out by Dr. Monrad-Krohn (6), and his description makes a link in a paper on the muscle connexions between auricle and ventricle in human hearts; a work for which the author obtained the University's gold medal. The investigations were so carried out that the calcareous encrustation with its immediate surroundings was cut out, divided into two pieces (I and II in Fig. 4), decalcified, embedded in celloidin and thereupon cut into serial sections, of which every third or every fourth section was examined after having been stained in acid haematoxylin (P. Mayer) and orange. As regards the results of the investigation we refer to the accompanying drawings (Fig. 5, *a*, *b*, *c*), and further we may add:

The pieces marked I and II (Fig. 4) were wholly cut into serial sections, frontally, beginning from the back and following the *a-v* bundle as it proceeds from atrium to ventricle; on an average every fourth section was examined. In the first sections the auricle muscles are seen to extend downwards along the right side of the beginning of the septum membranaceum. We here see how little by little the *a-v* bundle—the 'knot'—limits itself or tightens into a more collective mass, that on the other hand stands in direct connexion with the auricle muscles, which are here somewhat infiltrated with fatty tissue. In section No. 53 (Fig. 5, *a*) we see partly in the *a-v* bundle and partly in the surroundings certain small calcareous foci and lymphocytic infiltrations, and in the following sections we observe how the calcareous masses assume a larger and larger space, so that those in Fig. 5, *c* (section No. 65) take up the whole site of the *a-v* bundle. This is seen even more clearly in Fig. 5, *d* (section No. 10), in which the whole site of each *a-v* bundle is represented essentially by a large hollow (as the result of decalcification), and where corresponding to the calcareous knot, visible to the naked eye, we can see the endocardium prominent to the right. We find no trace of the *a-v* bundle in both these figures. All the figures are diagrams from drawings of preparations with Leitz drawing ocular (ocular I, objectiv I).

It appears from the investigations that the main trunk of the *a-v* bundle vanishes entirely in the large calcareous mass which forms the contents of the large prominence, the size of a pea, so clearly seen macroscopically in Fig. 4.

In complete agreement with these anatomical changes are the tracings previously discussed, which were taken from the patient and where the regular signs of a complete heart-block appear (Figs. 1 and 2).

What meanwhile is not in complete agreement with the said changes is in the first instance the tachycardia, which appears immediately after the more severe attacks, and in the second instance certain tracings which were taken between the attacks towards the end of the patient's life, and which appear to

show that co-operation between the auricles and ventricles was *not* quite broken off.

First *the tachycardia*. It has usually been taken for granted that the automatically working ventricle acts at a maximum speed of 40 beats per minute.

Mackenzie (5) says that if the ventricular contractions are over 36 per minute there cannot be a complete block between auricle and ventricle, and if the frequency is below 30 then the ventricular contractions probably are independent of the auricle; and Hering and others express similar opinions. There are, however, some experiences which appear to show that the action of the heart at least periodically may attain a greater frequency, even if the stimulus conduction through the *a-v* bundle is rendered impossible. First and foremost is remarkable in this respect a case which Aug. Hoffmann (3) relates in his lecture on 'Anatrie' heart-action, where according to the description there were clinically signs of a complete heart-block, and where the microscopic post-mortem examination shows 'deep destruction of the *a-v* bundle and its branches, amongst which old sclerotic scars, fresh infiltrations, together with new and old hemorrhages'. The pulse of this patient was usually slow (sometimes right down to four beats per minute), and he was suffering from syncopal attacks with convulsions; but sometimes after these attacks the speed of the ventricular contractions rose considerably—up to 120 contractions per minute, partly regular, partly irregular.

A case described by Heineke, Müller, and Hösslin, (2) also is to be mentioned in this connexion. Here the pulse rate sometimes rose to 72 beats per minute, and a distinct relationship between the ventricular and the auricular waves in the jugular pulse was evident in the tracings, though the post-mortem examination proved that the *a-v* bundle was completely destroyed by fibrous tissue partly calcified.

We could produce other cases from literature, even if not so convincing as the above, in which the heart, in spite of an existing ventricular automatism, periodically beats with considerably greater rapidity than we usually see in such conditions. The last two cases here reported appear at any rate to show—even if not quite to prove—that, on the one hand, ventricular action can be frequent in spite of the destruction of the *a-v* bundle, and, on the other hand, that co-operation between auricle and ventricle is not necessarily dissolved because the *a-v* bundle has been put out of action.

Also in the case described here, where the post-mortem examination compels us to assume that the relationship between auricle and ventricle along the *a-v* bundle must have been quite broken for a long time before death, and where also all the signs of a complete block have long been present, there occur attacks of great frequency of the pulse. And the tracings from the last weeks of the patient's life show that the stimulus conduction from auricle to ventricle must have been to some extent restored, though the result of the post-mortem a little later makes it more than probable that the main trunk of the *a-v* bundle must have been, so to say, cut across by the large calcareous knot.

We have no tracings from the more serious attacks, but Figs. 6, 7, and 8 were taken shortly after the first, third, and fourth attacks. These show, as regards Fig. 6, the numerous extra-systoles which vanished when the heart-action again became quiet. Fig. 8 shows the radial tracing below; the upper tracing is from the spot over the left jugular vein (just above the clavicle) from whence, in the case of this patient, it was otherwise always easy to obtain clear jugular tracings, but where just after the more severe attacks we could never obtain any distinct phlebogram. The tracing was taken ten minutes after the third attack, that is, about three weeks before the patient's death.

These tracings thus do not show us the condition of the pulse in the neck vein *during* these attacks. But besides the more severe attacks the patient had also a number of abortive attacks without loss of consciousness. The appearance of the venous pulse during these abortive attacks will be seen from Fig. 9, and especially from Fig. 10. In the latter the auricle is seen to beat quite regularly, as long as the intermission lasts (it lasted, however, somewhat longer than the tracing shows, the paper being too short to take the whole of the intermission). Fig. 9 also shows another phenomenon; the first part of the tracing shows a clear and constant relation between the contractions of auricle and ventricle, so that before each *c* wave in the jugular tracing there is a clear *a* wave, the distance of which from the *c* wave is everywhere about the same, that is, three-fifths of a second. The same can also be seen in the other tracings taken on the same day. Comparing the first part of this tracing with Fig. 1, we notice a striking difference: in Fig. 1 the auricle and ventricle beat separately without any demonstrable regular relationship; in Fig. 9 the ventricle contractions appear to be directed by the auricle contractions, even though the period taken to convey the movement from auricle to ventricle is abnormally prolonged. Thus in the one tracing total block, in the other a greatly injured conductivity. The tracing in Fig. 9 was taken seventeen days before the patient's death, that is, at a period when we quite certainly may assume from the results of the microscopic examinations that the stimulus conduction through the *a-v* bundle had been rendered impossible. It appears then as if in this case, as in the one earlier discussed of Heineke, the stimulus has been conducted from auricle to ventricle in spite of the fact that the trunk of the *a-v* bundle was destroyed right through its transverse section. It cannot be said by what track this conduction has gone, for we have searched in vain for muscular connexion in the place of the *a-v* bundle. It is noteworthy that it was only in the last weeks of the patient's life that signs appeared of such a connexion, for previously the tracings had always an appearance that, as in Fig. 1, showed an unquestionably complete dissociation.

Neither can it be said with certainty in what manner the tachycardial attacks were brought about. Hoffmann (l. c., p. 623) believes that the ventricle, the relationship between auricle and ventricle being broken, beats with a different rate and rhythm from regular bradycardia to regular tachycardia, eventually with extra-systolic arrhythmia or complete irregularity.

In the case here referred to as explanation of the periodical paroxysms of tachycardia, the possibility of a conduction of the stimulus outside the  $\alpha$ -v bundle is to be mentioned (cf. the relationship between auricular and ventricular function appearing in the tracing in Fig. 9).

Not many cases are known where the trunk of the  $\alpha$ -v bundle has quite surely been destroyed right through its transverse section, and where also exact tracings from veins and arteries have been taken.

Nagayo mentions in his work from 1909 that he has found only four cases of Adams-Stokes disease which have been exactly investigated anatomically, and in which the  $\alpha$ -v bundle was completely destroyed. In the case of two of these (Keith and Miller's case and Lucas and Fahr's) the tracings are lacking, and in the remaining two (Ashton's and Heineke's) we find both tracings and anatomical examinations. To these four cases Nagayo adds his own, without tracings. The result of the clinical and anatomical examination in this case seems to indicate that the conduction of the stimulus is not only and exclusively a function of the  $\alpha$ -v bundle: there must exist some other ways for this conduction under certain circumstances. In this regard our case is a supplement to the case of Heineke mentioned on p. 501.

#### Case No. II.

*Adams-Stokes syndrome with normal  $\alpha$ -v bundle, but strongly pronounced degenerative neuritis in both vagus nerves. Diabetes mellitus.*

The patient, a man 54 years of age, who had always been in good health, free from alcoholic intoxication and syphilitic infection, began to feel weak some months before his death; he had two or three brief attacks of fainting, and the physician he consulted on this account found 5 per cent. of sugar in his urine. He was put on diabetic diet, the sugar disappeared, and the patient got on very well on the whole until about one week before his death, when one day he suddenly had a series of fainting fits. He was at once taken to the hospital, where he arrived in such a serious condition that no complete examination could be undertaken. One fainting fit succeeded another at quite short intervals. The longest of the syncope attacks lasted about one minute. Between the attacks the pulse frequency was about 26; the pulse was regular and full; during the attacks it was at times slower and at others completely disappeared. The respirations during the attacks were to some degree deeper and strongly stertorous, whilst during the shorter attacks respiration completely stopped and showed indications of the Cheyne-Stokes type. During the first night in the hospital the patient had up to twenty-seven fainting fits per hour.

The day following his admission to the hospital (Oct. 31, 1907) his condition was practically unchanged, but the attacks were now more severe. There was, however, at times so long intervals between them, that a more complete examination could be accomplished.

The patient was a strong, well-built, and well-nourished man. Between the attacks the pulse-frequency varied from 24 to 80 (just after an attack). No apex beat could be felt, the heart-sounds were normal, the action of the heart nearly regular, and of the same frequency as the radial pulse. The heart dullness was somewhat large. No plain venous pulse could be seen in the neck. The urine contained no albumin, but 5.9 per cent. of sugar, no diacetic acid, sp. gr. 1035.

During the eight days that the patient lay in the hospital, there occurred a series of attacks which came partly incessantly one after the other, partly



with some hours' interval between them. All the attacks appeared to be somewhat similar. The more severe began with the disappearance of the radial pulse. The patient became pale, moved his head from side to side once or twice, or else turned it to the right, and then lost consciousness often in the midst of a sentence he was uttering at the moment. Then respiration stopped or became weaker, the eyes half closed and the globes were turned upwards and to the right. After complete apnoea or quite superficial respiration had lasted for twenty to thirty seconds, respiration began strongly, stertorous, increasing in depth.

When a certain amount of strength of respiration had been attained, the radial pulse was suddenly felt, first some weak beats which then increased rapidly in strength and frequency. Immediately after the attack up to 80 beats in radial per minute were counted. Almost at the same time that the radial pulse began to be perceptible, or a little before, a strong flush suddenly passed over the pale face, he raised his eyes and consciousness suddenly returned, whilst he often asked if he had been asleep. During the attacks small convulsions were sometimes observed in both arms. At the beginning of an attack the pupils expanded; they contracted when the face became red towards the end of the attack. During the attacks no evident movement in the veins of the neck could be discerned. Between the attacks the pulse frequency, as already mentioned, was variable, commonly between 24 and 40; after the attacks it was more frequent, and on one occasion 80 beats were counted. The pulse was of high tension, sometimes regular, at other times irregular. On Oct. 31 the patient received, at 6, 8, and 11 o'clock p.m., 1 mg. atropine subcutaneously. The attacks, that had been incessant before the injections of atropine, became more rare after the second injection, although the injection had no perceptible effect on the pulse frequency. The injections of atropine were repeated several times on the following days, without other effect than that, as before said, the attacks perhaps became less frequent. After this condition had continued as described for eight days, the patient died with severe pain in the right side of the chest and dyspnoea. Previous to death the pulse was weak, with occasional frequency up to 100. The attacks were much less frequent in the last four days, and for two days he was entirely without attacks. At the post-mortem examination the heart was found to be hypertrophied, dilated, and to some degree infiltrated with fat; it weighed 510 gm.

The subpericardial fat was highly developed, especially over the right half of the heart, where the muscles were also somewhat infiltrated with fat without showing any signs of fatty degeneration. Incipient arterio-sclerotic changes in aorta were present. The coronary arteries normal. An embolus was found in the right pulmonary artery, with an incipient haemorrhagic infarct in the lung. The other organs were found in all essentials normal. The microscopic examination of the *a-v* bundle<sup>1</sup> showed that it was mixed with fatty tissue with large fat cells, perhaps to a little higher degree than is found on an average, but, however, not outside the normal limits. The fatty tissue was found especially in the main trunk and also in the left branch. The *a-v* bundle was also somewhat hyperaemic (a post-mortem phenomenon?), but not especially strongly marked. On the whole the *a-v* bundle presented no clear pathological alterations.

In both vagus nerves there were found *very important* anatomical changes.

In unstained preparations from the upper part of the nerves black drops of fat could be seen around the nerve.<sup>2</sup> In sections where the nerve is longitudinally cut, the fibres are to a large extent brownish-black to black. Such

<sup>1</sup> Examination carried out by Dr. Monrad-Krohn with the same method of investigation as in Case No. I. The whole main trunk of the bundle was examined in serial sections.

<sup>2</sup> The vagus on both sides of the neck was removed and from three points of the removed nerve sections were examined (from the upper, the middle, and the lower part of nerve-trunk). The vagi, as the other parts of the nervous system microscopically examined, were

black fibres are found partly through long stretches of the nerve, and they are on the whole rather homogeneous, although in places it gives the impression of a kind of accumulation of small granules of different sizes. In places where the section has been made across the nerve, we find, in addition to swollen black nerve fibres, a similar number of more yellowish normal fibres.

The middle portion of the neck vagus shows on the whole the same aspect as described above, but the black parts of the nerve fibres are seen to be more extensive, so that the majority of the nerve fibres are black; the black round or cylindrical formations are seen on closer inspection to be formed by numerous small granules or fragments.

In sections from the lower portion of the nerve (about where the cardiac branches come off), extensive black cylindrical formations were seen, consisting of extremely fine small black granules, lying spread in the larger bundles. (Cf. Fig. 11.)

Examination of the right vagus showed the same appearance as that described for the left.

In haematoxylin stained sections no signs of inflammation were to be seen. The right and left middle cervical sympathetic ganglion and the cardiac sympathetic ganglion, prepared in exactly the same manner as the vagus, showed nothing abnormal.

The medulla oblongata showed in the upper half of the fourth ventricle and in the lower half no degenerated nerve fibres. The ganglion cells at the bottom of the fourth ventricle, amongst which are the vagus nuclei, showed an extremely finely granulated grey-black coloration (lipochrome), but no signs of degeneration. The hypophysis showed its normal structure without any sign of inflammation or degeneration. (Professor Harbitz, Dr. Backer-Gröndahl.)

The chief interest in this case lies in the fact that in all probability it must be regarded as a case of Adams-Stokes disease of vagal origin. There is, however, a difference of opinion as to whether there may exist any certain case of Adams-Stokes disease of vagal origin.

A. Nayago, who appears to accept without further question a number of cases of Adams-Stokes disease from the older literature as being of vagal origin, reports from the newer literature one case of Levy, without post-mortem, and one of Lepine, also without post-mortem, as 'indubitable cases of neurogenous form'. At the French Congress for Medicine in 1910 Vaquez, after having discussed the bradycardias that are due to lesion of the a-v bundle, says there only exist two certain observations of Stokes-Adams disease which can be referred to the vagus. One of these is described by Esmein (1), the other by Laslett (4). So far Vaquez. But Hering says, about the same period, during the discussions in the German Medical Congress (cf. *Verh. des deutschen Kongresses f. inn. Med.*, 626), that in his opinion no certain proof that Adams-Stokes disease can be of neurogenous origin has so far been produced.

In these circumstances we may be allowed to recapitulate the main features in Esmein's and Laslett's cases. Esmein's patient was 23 years of age, and presented the appearance of an Adams-Stokes bradycardia with syncopal attacks. The following characteristics were present:—

prepared in this manner: fixation in formol for several days, then for a couple of weeks in Müller's liquid, then for a week in osmic acid and sodium iodate solution; washing and embedding in celloidin. The sections were examined partly not stained, partly stained in haematoxylin. The necropsy was made fifteen hours after the death, in the winter.

1. The *bradycardia*, although usually present, was not permanent. Now and then, especially when the patient awoke after the attacks, the pulse frequency attained a normal height ('comme si la reprise du fonctionnement actif des centres nerveux avait eu une influence déterminante sur la production de la bradycardia'). During a febrile illness the bradycardia disappeared, and it also disappeared during a brisk walk (there even then appeared a passing tachycardia). Moreover, bradycardia regularly disappeared when atropine was injected.

2. The bradycardia was always moderate, never under 40.

3. It was never possible to observe the ordinary signs of total dissociation in the tracings, but the latter showed various other abnormalities in the heart action. Thus at one time an incomplete dissociation between auricle and ventricle could be proved, at another time an auricular contraction failed to appear in front of a ventricular systole, or, again, there was a true total bradycardia which comprised the whole heart. According to Esmein these characteristics agree fully with the bradycardia, which can be produced experimentally by the irritation of the vagus. Esmein therefore considers himself justified in believing that such vagus inhibition occurs in his case, and, supported by the result of the Röntgen examination, he believes that it has been caused by a roundish tumour in the mediastinum at the base of the heart just where the vagus nerves branch into a net to contribute towards the formation of plexus cardiacus (he believes the tumour to be tuberculous glands).

Laslett's patient was 40 years of age; for some years she had suffered from periodic attacks of fainting. During the period of the attacks the pulse was 32-40, otherwise about 66. The bradycardia was produced by long intermissions during which the whole heart stood still, and thus presents a different phenomenon from that present in heart-block. In Laslett's case, in opposition to Esmein's case, the jugular and apex tracings show that constantly neither auricle nor ventricle beat during the intermissions; there was *always* a pause of the whole heart, and the  $\alpha$ -c interval shows very little variation; particularly there is no change after the intermission, and therefore there can be no diminution of conductivity in the  $\alpha$ -v bundle. Laslett forms two conjectures as possible explanations of the phenomena: (1) A block between the sinus and the auricle, or (2) Depression of the sinus rhythm by vagus inhibition.

He concludes that the slow pulse and the intermissions are the result of increased vagus influence on the sinus rhythm—a primary chronotropic effect (that is therefore of the same nature as Mackenzie's 'youthful type of irregularity'). He supports his opinion by the following:—

1. Atropine makes the bradycardia disappear.
2. By swallowing, the pulse quickens.
3. The staircase phenomenon is sometimes seen after the intermissions.
4. Anaerotism of the pulse may sometimes be observed after the intermissions.

So far as concerns the cause of the increased vagal action, Laslett can

express no decided opinion. In none of these cases have we any post-mortem examination before us.

A comparison between our case and the cases described by Esmein and Laslett shows both conformities and dissimilarities. The bradycardia in all three cases is exceedingly inconstant; but it sinks in our case sometimes to much lower degrees than in the two other cases. How the bradycardia varies in our case, may be seen by the following:—

Oct. 30, evening,	the radial pulse beats	20-26
Oct. 31	" "	40-80
Nov. 1	" "	24-60
Nov. 2	" "	about 50
Nov. 3	" "	30-40
Nov. 4	" "	40
Nov. 5	" "	36-44
Nov. 6	" "	36
Nov. 7	" "	100

In our case the bradycardia was not plainly influenced by atropine; but perhaps the missing effect of the atropine injection is due to the small dose (1 mg.). By examining some of the many tracings taken during the patient's stay in the hospital there may be seen in Fig. 12 a long intermission in the radial tracing, and just after the intermission there is a distinct indication of the staircase phenomenon and not only the contractility successively is seen increasing, but also an increasing chronotropic effect is to be supposed. On the whole the aspect of this tracing involuntarily calls to mind the effect of the experimental vagus irritation. In Fig. 13 there is a distinct incomplete dissociation; one can see in the jugular tracing many an isolated *a* wave without its normal *c* wave, but there is always an *a* wave before every *c* wave. In Fig. 14 is seen almost the same form of the tracing as in Fig. 12, but the distances between the blockaded and the not blockaded *a* waves change quite regularly. Finally, Fig. 14 shows quite another aspect, the bradycardia partly being here total, including both auricles and ventricles, partly showing the aspect of a heart-block.

Regarding the high variability of the bradycardia, some of the features in the tracings (for instance the staircase phenomenon, the increasing chronotropic influence after the intermission, &c.), and the considerable pathological changes in both the vagi, it is highly probable that the origin of the clinical symptoms in the first instance is to be sought in the vagus affection.<sup>3</sup> If this conclusion is right, the case is to be considered a case of Stokes-Adams disease of vagal origin, where—different from the cases described by

<sup>3</sup> The question might perhaps also be discussed if there is some relation between the glycosuria and the vagal neuritis. On the one hand the diabetic neuritis is well known, on the other is involuntarily called to mind the celebrated experiment of Cl. Bernard, when he, having cut the vagus nerve, produced glycosuria by irritation of the central end.

Esmein and Laslett—first, the bradycardia sometimes goes far below 40, and, secondly, the bradycardia is not abolished by atropine. If the vagal origin of the bradycardia in our case is not accepted, one is obliged to seek the explanation of the symptoms in a functional insufficiency either in the  $a-v$  bundle or in other parts of the heart muscle. By examining the  $a-v$  bundle there is revealed no plain pathological changes, and the muscular (extra-fascicular) type of the disease of Stokes-Adams, that is specially described by Pletnew and Nayago, has still to be proved in man.

## REFERENCES.

1. Esmein, *Bull. et Mém. Soc. méd. des hôp. de Paris*, 1910, 848.
2. Heineke, A., Müller, A., and Hösslin, H., *Deutsch. Archiv f. klin. Med.*, Leipz., 1908, xciii, 475.
3. Hoffmann, A., *Verh. d. deutschen Kongr. f. innere Med.*, 1910, 616.
4. Laslett, *Quart. Journ. of Med.*, Oxford, ii, 347.
5. Mackenzie, J., *Diseases of the Heart*, Lond., 1908, 169.
6. Monrad-Krohn, G. H., *Norsk. Mag. f. Lægevidenskaben*, 1910.
7. Wenekebach, K. F., *Archiv f. Anat. u. Physiol.*, Leipz., Physiol. Abt., 1906, 335.

## DESCRIPTION OF FIGURES.

PLATE 41, FIG. 1. Case I. The tracing shows a complete heart-block (the upper tracing from the jugular vein, the undermost from radial).

FIG. 2. Case I. The upper tracing from the liver, undermost from radial.

FIG. 3. Case I. Intermission without loss of consciousness.

PLATE 42, FIG. 4. Case I. The interior of the right auricle and ventricle.

PLATE 43, FIG. 5. Case I. Fig. 5,  $a$ ,  $b$ ,  $c$  are sections from the piece marked I in Fig. 4. Fig. 5,  $d$  is from the piece II in Fig. 4. In all figures :

$a$  = auricular muscle.

$f$  = fatty tissue.

$a-v$   $b$ . =  $a-v$  bundle.

(As to the examination technique, see p. 500.)

PLATE 44, FIG. 6. Case I. Tracing taken after the first attack (Jan. 27, 1907); the upper tracing from the apex.

FIG. 7. Case I. Tracing taken ten minutes after the second attack.

FIG. 8. Case I. Tracing taken immediately after the third attack (upper jugular, lower radial).

FIG. 9. Case I. Jugular and radial tracing. A long radial intermission, during which the movements in jugular continue.

FIG. 10. Case II. Jugular and radial tracing. During a long radial intermission the auricle is seen to contract regularly.

PLATE 45, FIG. 11. Case II. Section from the left vagus nerve.

PLATE 46, FIG. 12. Case II. Radial tracing.

FIGS. 13, 14, 15. Case II. Radial and jugular tracing.



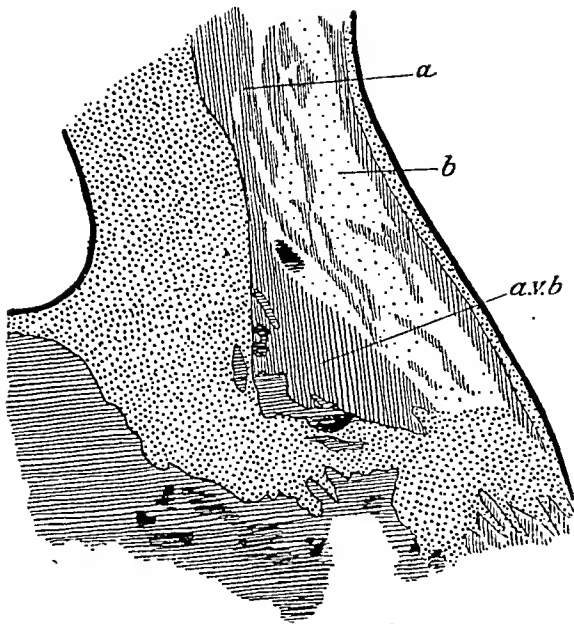




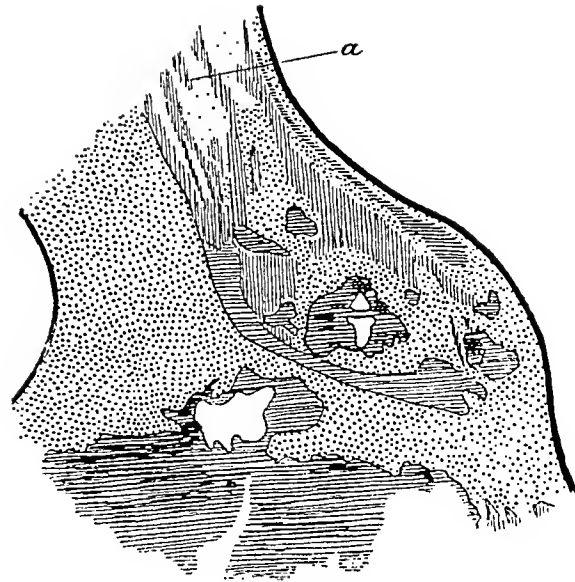
Fig. 4 (Case I)



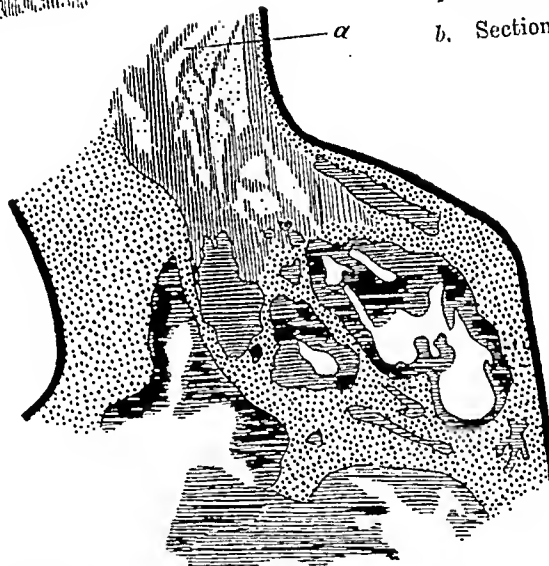




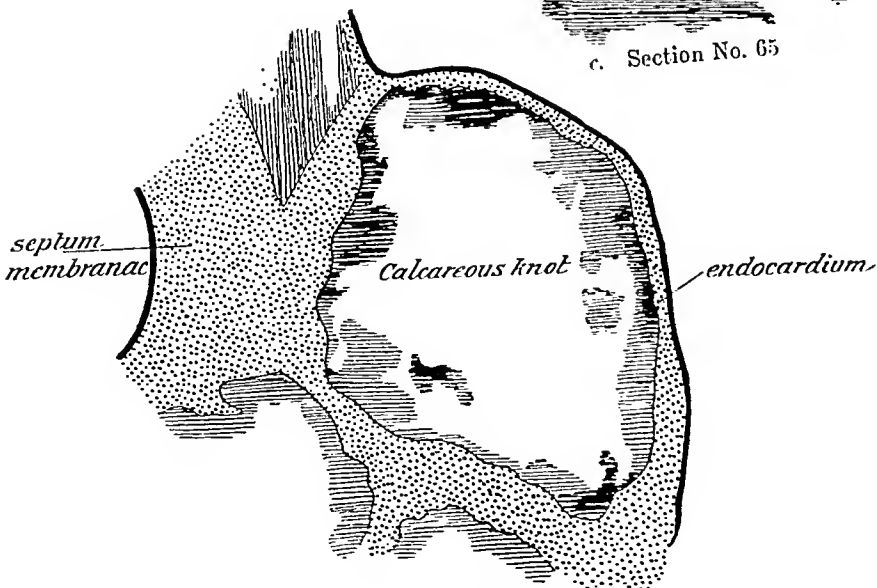
a. Section No. 53



b. Section No. 62



c. Section No. 65



d. Section No. 10





FIG. II (CASE II)



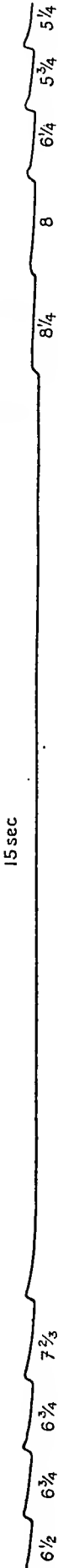


FIG. 12 (Case II)



FIG. 13 (Case II)

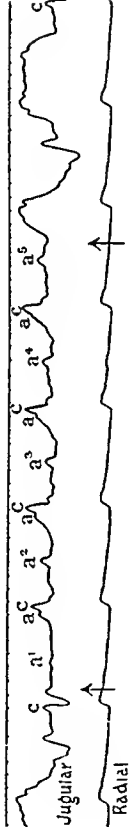


FIG. 14 (Case II)

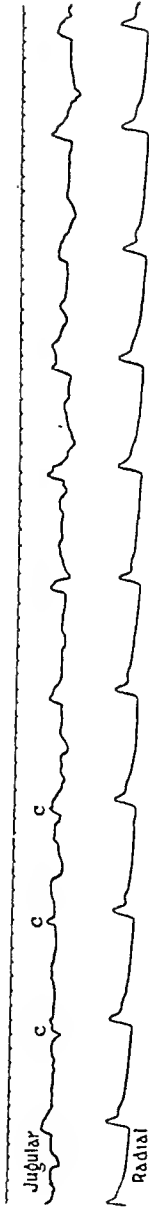


FIG. 15 (Case II)



# ESSENTIAL RENAL HAEMATURIA

By W. HALE WHITE

MANY a time it has happened that a physician or surgeon has, on account of haematuria or pain in the neighbourhood of one kidney, thought that a stone or new growth existed in this organ, but a most careful exploration, or in some cases excision of the kidney, has failed to find either, or any satisfactory explanation for the pain or haematuria. Pain felt near the kidney may be due to so many causes that I shall not consider it here, but it is of interest to know that during the seven years 1904-1910, both inclusive, there were, on the surgical side of Guy's Hospital, ten patients (six males and four females) suffering only from pain in the renal region, which was sufficiently characteristic and severe to justify exploration of the kidney in the hope of finding a stone, but none was found. In not one of any of these ten was there any haematuria, in three the report does not mention the result of the X-ray examination, in the remaining seven the X-rays did not show a stone. All the patients were under 45, one was a boy 9 years of age, the next youngest was 21 years old.

Pain is, however, often associated with haematuria in the cases about to be described, namely, those in which the patient suffers from haematuria, usually only from one kidney, which is not due to any of the well understood causes of bleeding from the kidney. He is then said to be afflicted with 'essential renal haematuria', a name that will serve until the cause of the bleeding is discovered. Other names have been employed, e.g. renal epistaxis, but the greater number of writers use 'essential renal haematuria' ('essentielle Nierenblutung'). The disorder has given rise to much interest in Germany, to some in America, to slight in France, and to very little in England. It is true that a few single cases have been recorded in this country, but the subject is dismissed in a few lines by Morris,<sup>1</sup> who mentions a fatal case of his own in which neither by the naked eye nor with the microscope could anything wrong be found in the kidney although it had bled. 'Essential renal haematuria' is hardly ever mentioned in any English textbooks, and the only two important articles published on the subject in England are by two foreigners, Schüller<sup>2</sup> and Rosving.<sup>3</sup>

<sup>1</sup> H. Morris, *Surgical Diseases of the Kidney and Ureter*, London, 1901, i. 591.

<sup>2</sup> Schüller, 'A Clinical Lecture on Essential Nephritic Haemorrhage,' *Med. Press and Circular*, Lond., 1906, lxxxi. 62-4.

<sup>3</sup> T. Rosving, 'On Obscure Haemorrhage from a Single Kidney and its Cure by Nephrotomy,' *Brit. Med. Jour.*, 1898, ii. 1547-50.



It is, however, described by Senator<sup>4</sup> in Nothnagel's *Encyclopaedia*. He says: 'There still remains a group of cases in which nothing can be found in the kidneys to account for the haemorrhages and the accompanying continuous or paroxysmal pain; these have been called cases of essential renal haemorrhage.' He then alludes to cases of venous angioma of the papillae and goes on: 'In other cases more or less extensive inflammatory processes have been found in the kidneys, and the haemorrhages have therefore been ascribed to a haemorrhagic nephritis. But in some of these cases it had evidently subsided long before, so it is not probable that these changes had any casual connexion with the haemorrhages. Such cases, and a few others in which no changes and certainly no nephritic processes could be detected even with the aid of the microscope, suggest that these essential haemorrhages depend on a nervous disturbance, and are either angioneurotic or neuropathic.' The editor of the English translation, James B. Herriek, states in a note to Senator's description, that he has seen painless haematuria in a man of 45, the bleeding having lasted for ten months. The cystoscope showed that the blood came from the right kidney. Nephrotomy revealed nothing abnormal. The kidney was normal histologically. The haemorrhage ceased ten days after the operation, and five or six months later had not returned although the man was at work. It is necessary to bear in mind that essential renal haematuria has, as Senator says, nothing to do with haematuria of an angioma or capillary naevus of a renal papilla. Hurry Fenwick<sup>5</sup> described six of these cases and Whitney<sup>6</sup> and Hugh Cabot<sup>7</sup> both give excellent drawings of the histological appearances of one of these bunches of minute varicose veins from cases, in which they led to profuse bleeding. I have seen two cases, and within the last seven years there have been three cases in Guy's Hospital I have not seen. The haematuria may be very profuse and last indefinitely. There is normally a plexus of minute veins at the apex of each papilla, and under certain circumstances which we do not understand these become enlarged and from them haemorrhage ensues. The condition may be suspected if the patient has no other symptom than continuous haematuria, but a correct diagnosis can only be made after the pelvis of the kidney has been opened. For the best way of dealing with this condition the reader is referred to Fenwick's book. As far as we know the bleeding only stops after operation.

To return to the subject of essential renal haematuria. There is such an extensive literature about it that it would be wearisome to go through the whole of it. Kretschmer<sup>8</sup> published a valuable paper in 1907 and gives a list of references to eighty-five papers, but the case of his own which forms the basis

<sup>4</sup> Nothnagel's *Encyclopaedia of Practical Medicine*, English Edition, Vol. on Diseases of the Kidneys, &c., Philadelphia and London, 1905, 54.

<sup>5</sup> Fenwick, *Clinical Cystoscopy*. London, 1904, 392.

<sup>6</sup> Whitney, *Boston Medical and Surgical Journal*, 1903, clviii. 797.

<sup>7</sup> Hugh Cabot, *American Journal of Medical Sciences*, 1909, cxxxvii. 94.

<sup>8</sup> H. L. Kretschmer, 'Beitrag zur Frage der essentiellen Nierenblutung,' *Zeitschr. f. Urologie*, 1907, i. 490.

of his paper cannot be regarded as undoubtedly one of essential renal haematuria. The patient, a boy aged 17, had haematuria which the cystoscope showed to be due to bleeding from the left kidney. Nephrotomy was done and the bleeding ceased for a time. A piece of the kidney was excised and Kretschmer considered it showed slight inflammatory changes, but some who discussed the case at a meeting of the Gesellschaft der Ärzte in Vienna doubted whether it did. Eighteen months later, the bleeding having returned, the kidney was excised and then undoubtedly showed chronic inflammatory changes. Kretschmer uses this case as an argument that essential renal haematuria is really due to a nephritis, but it seems to me, considering the possible histological changes found at the nephrotomy, considering the fact that the patient had had scarlet fever, and considering that even before the first operation urine collected with a separator only from the right kidney showed albumin, he really here was dealing with a case of scarlatinal nephritis. Even if this suggestion could be disproved it would be possible to argue that the decapsulation and excision of a piece of kidney at the first operation had induced the nephritis found eighteen months later when the kidney was excised. He collected from literature 129 cases which might perhaps, he thinks, be regarded as essential renal haematuria. In 61 there was a histological examination of a piece of the kidney, in 52 of these there was evidence of some nephritis or analogous changes, and he suggests that in the remaining nine such might have been found if they had been looked for more carefully. The criticism which may be passed upon this is that in many cases the histological deviation from the normal was very slight, that even then it may not have been the cause of the haematuria, that it is quite conceivable that bleeding into the kidney might after a time lead to histological changes in it. Kretschmer, although sceptical about the existence of essential renal haematuria not due to nephritis, does not deny it; indeed he suggests it may be due to autotoxaemia. Like other authors he considers that decapsulation or nephrotomy is of great benefit for this condition.

At the end of this paper I have given the literature of the subject since the publication of Kretschmer's paper and will only allude briefly to the more important papers which appeared before 1907. Schüller,<sup>9</sup> in a critical paper, describes the case of a woman, aged 49, who had severe haematuria from the right kidney; the urine from the left contained no albumin. The specific gravity was 1.020, there were no casts. There was no clinical sign of nephritis. Nephrotomy was performed. A year later the haematuria had not returned. To the naked eye the kidney seemed healthy, and from the description of the histological appearances of an excised piece I think the organ can hardly be considered abnormal, and certainly not sufficiently so to account for the haematuria, for the kidney is stated to have been normal except for a few microscopic cysts and some free epithelium in a few tubes. Schüller, however, considers that the haematuria should be ascribed to nephritis in this and also in

<sup>9</sup> H. Schüller, 'Beitrag zur Lehre von den Blutungen aus anscheinend unveränderten Nieren,' *Wiener klin. Woch.*, 1904, 477.

other published cases of essential haematuria. His patient did not menstruate during the haematuria nor after it had stopped.

Rosving's<sup>10</sup> paper contains a very good discussion of some unusual causes of haemorrhage from one kidney, although considering the rarity of renal haemorrhage and the frequency of tight lacing I think we may doubt whether this is ever a cause as he suggests. His third case appears to have been an example of essential haematuria. The patient was a man aged 47; the urine from the left kidney contained blood, that from the right was healthy. At a nephrotomy operation the kidney appeared perfectly normal; after the operation the haematuria ceased, and had not returned six months later. Rosving and many other authors consider that Klemperer's<sup>11</sup> patient was an example of genuine essential renal haematuria. The patient, a young man aged 22, had haematuria which proceeded, as shown by the cystoscope, from the left kidney. Nephrectomy was done and the kidney was perfectly healthy both to the naked eye and microscopically. Klemperer supports the view that the bleeding is angioneurotic and discusses the possibility that some cases are examples of vicarious menstruation. Wulff's<sup>12</sup> case, too, is a good example of one generally allowed to be an instance of essential renal haematuria. The patient, a male aged 46, had seven years previously a similar illness, from which he recovered. When seen by Wulff there had been haematuria for eight months; the blood came from the right kidney, the urine from the left was normal. A nephrectomy was done; the excised kidney, both to the naked eye and the microscope, was perfectly normal. The bleeding ceased completely three days after the operation, so the blood could not have come from the ureter, down which a catheter passed normally at the operation, and to the cystoscope the orifice of the right ureter was healthy. The fact that the patient had a similar attack seven years before and yet now the kidney was healthy is a strong argument against the possibility of the bleeding having been due to nephritis. Schenck's<sup>13</sup> is an important case, for the patient, a woman aged 46, had haematuria and haemorrhage from the left kidney; the bleeding ceased gradually after a nephrotomy. A piece of kidney was excised and appeared perfectly normal when examined histologically.

One of the most important papers of those without a microscopical examination of the kidney previous to 1907 is that by Harris.<sup>14</sup> His first case is that of a car conductor, aged 51, who was temperate. Haematuria was first noticed in 1895. No pain, urine no casts. Sp. gr. 1.018. After some months the patient became very weak from continual loss of blood, which ceased after rest in bed. He returned to work and worked hard in perfect health for two and a half years without any loss of blood. He then passed out of observation. He was not a sufferer from

<sup>10</sup> T. Rosving, 'Obscure Haemorrhage from a Single Kidney and its Cure by Nephrotomy,' *Brit. Med. Jour.*, 1898, ii. 1547.

<sup>11</sup> Klemperer, 'Ueber Nierenblutungen bei gesunden Nieren,' *Deutsch. med. Woch.*, 1897.

<sup>12</sup> P. Wulff, 'Zur Kasuistik der essentiellen Nierenblutung,' *Münch. med. Woch.*, 1903, 1257.

<sup>13</sup> B. R. Schenck, *Medical News*, New York, 1904, lxxxv. 1206.

<sup>14</sup> M. L. Harris, 'Renal Haematuria without Known Lesions,' *Phila. Med. Journ.*, 1898, i. 509.

haemophilia, and I do not think the bleeding can have been due to varicose veins of the papillae as it stopped; there was no evidence whatever of any variety of nephritis. Harris's second case is that of a man aged 50, temperate, and not a sufferer from haemophilia. He had had haematuria for three years. The cystoscope showed the blood to come entirely from the left kidney. No casts. Sp. gr. 1.030. Nephrotomy, the kidney appeared perfectly normal. The haematuria ceased after operation, and when the patient was last heard of six months after operation there was still no blood in the urine. Harris gives many references, discusses the subject, and considers that essential renal haematuria is a definite disease. Schüller<sup>15</sup> describes a case of nephrotomy for bleeding from the right kidney, in a man aged 21. No casts. The bleeding ceased after operation and had not returned five months later; no cause for the bleeding was found. At the operation the kidney seemed to the naked eye quite healthy. He records another case which suggests that the bleeding may sometimes occur from one kidney and sometimes from the other in patients who suffer from essential renal haematuria, but I should have said after reading the literature of the subject that this rarely happens, for a nephrotomy performed upon the kidney from which the cystoscope shows the blood to come, usually leads to a cessation of the haematuria, which it would not do if the bleeding came at times from one kidney and at times from another. Schüller discusses the possibility of ordinary nephritis being sometimes unilateral and therefore explaining these cases, but he points out that Kummel catheterizing both ureters in 100 cases of Bright's disease did not find one in which the disease was unilateral. Fowler's<sup>16</sup> paper is chiefly interesting for his discussion of the various views held by different writers upon the subject of essential renal haemorrhage. His case was certainly not an example of this condition and he doubts whether it exists. Elliott's<sup>17</sup> case is of interest because the X-rays gave evidence of a stone in the left kidney. There was haematuria, but a thorough examination at a nephrotomy failed to show any stone and the haemorrhage ceased after operation and had not returned six months later. He states that Rayer,<sup>18</sup> writing in 1841, devotes much attention to essential renal haemorrhage. The French papers on the subject hardly call for any notice.

The following are the more important papers which have been published since Kretsehmer's. Steinthal<sup>19</sup> records the case of a girl, aged 22, whose left kidney was excised on Feb. 23, 1906, for haemorrhage. Baumgarten reported that there were no abnormal changes in the organ; there was blood in the tubes and glomeruli, the epithelium was intact, there were no changes in the vessels. Steinthal considers shortly other published cases and refers to

<sup>15</sup> Schüller, *Med. Press and Circ.*, 1906, lxxxii. 62.

<sup>16</sup> H. A. Fowler, *New York Med. Journ.*, 1905.

<sup>17</sup> Elliott, *International Clinics*, 1906, iv. 122.

<sup>18</sup> Rayer, *Traité des Maladies des Reins*, Paris, 1841.

<sup>19</sup> Steinthal, 'Zur Kenntnis der essentiellen Nierenblutungen,' *Beiträge zur klin. Chir.*, 1907, liii. 772.

two of those published by Caspar,<sup>20</sup> one a man aged 57, who for nine weeks had passed blood in the urine from the left kidney, which was excised and was perfectly healthy to the naked eye and on microscopical examination; the second case was that of a woman, aged 27, who had severe haemorrhage from the right kidney, which was excised and examined histologically. Very trifling changes were found, and these were quite inadequate to explain the haemorrhage.

Heymann<sup>21</sup> gives the case of a girl, aged 19, who had passed bloody urine for four years. No treatment did any good. The blood came only from the left kidney. Decapsulation and nephrotomy were done on this; after operation the patient gained in weight, and the bleeding ceased. Three months later it had not returned. The kidney was not examined microscopically, but it appeared healthy to the naked eye.

Kotzenberg's<sup>22</sup> is an important paper. Out of 400 operations on the kidney 12 were done for severe unilateral renal haemorrhage without finding at the operation any appreciable cause for the bleeding. Four were nephrectomies, 6 nephrotomies, and 2 decapsulations. One of the nephrectomies died. Only 3 of the cases were over 30 years of age; 10 were males, 2 females. There was nothing in the previous histories to suggest a cause for the trouble. There were no clinical symptoms except haematuria and such debility as might be caused by it, and sometimes a little pain in the back. The character of the urine was rarely such as to suggest nephritis, no casts or at most a few hyaline ones, specific gravity normal, albumin only proportionate to blood, and no albumin in the urine from the kidney which was not bleeding; in two cases examined bacteriologically the examination was negative. There was nothing in the general symptoms to suggest nephritis. He believes that in essential renal haematuria haemorrhage is the first symptom of a nephritis, and he quotes Kretschmer's case, which I have already given, and one of his own in support of this view. He believes the bleeding is due to a toxic nephritis, always bilateral, but that at the time of observation only one kidney happens to be showing symptoms; for this reason he is opposed to nephrectomy (unless the severity of the bleeding renders it absolutely essential), for it may lead to uraemia. The nephritis, which usually shows only on microscopical examination, is seen in the cortex and affects chiefly the capillaries. Decapsulation is the best treatment. Details are given of each of his twelve hospital cases and one private case. It might be urged that some of them were not strictly examples of essential renal haematuria—for example, Case XII was probably suffering from chronic nephritis of both kidneys—yet there is no doubt they form a remarkable series. For the urine from both kidneys was examined; that from one contained blood, while that from the other in almost all contained neither blood nor albumin, and the frequent absence of casts from the urine of both sides is very striking. But Case VIII is

<sup>20</sup> Caspar, 'Ueber ungewöhnliche Nieren- und Nierenbeckenblutung,' *Arch. f. klin. Chirurg.*, lxxx.

<sup>21</sup> A. Heymann, *Deutsch. med. Woch.*, 1907, xxiii. 325.

<sup>22</sup> W. Kotzenberg, 'Ueber Nierenblutungen,' *Zeitschr. f. Urologie*, 1908, 125.

difficult to understand, for the urine contained no casts, that from the right kidney was healthy, that from the left contained blood; the patient, aged 24, had had scarlet fever followed by haemorrhagic nephritis three years before. The left kidney, which was excised on account of severe bleeding from it, showed chronic interstitial nephritis. In such a case it is highly probable the nephritis was due to the scarlet fever, yet there were no casts and the urine from one kidney was healthy.

Hildebrandt<sup>23</sup> records a case of one-sided renal haemorrhage. Nephrotomy was performed, the kidney appeared healthy and a piece excised was healthy histologically. The bleeding ceased after operation. Spitzer<sup>24</sup> gives an interesting case of a young woman who in 1902 had so much blood in the urine that she was profoundly anaemic. By examination with a cystoscope and separator this was seen to come from the left kidney, the urine from the right being clear. Operation was contemplated but not undertaken, the bleeding ceased, the patient became quite well and was still so seven years later.

Bleek<sup>25</sup> writes a long article, chiefly of value as he gives the various views as to the cause of essential renal haematuria and also many references.

Ritter<sup>26</sup> records the case of a man, aged 64, who had pain over the right kidney; this was felt to be enlarged, and there was blood in the urine from it but none in that from the left. The X-rays did not show a stone. A nephrotomy showed the kidney to be healthy to the naked eye and a piece excised was healthy when examined histologically.

Senator<sup>27</sup> thinks that renal haemophilia exists and that renal haemorrhage may be the only evidence of it, and this without any evidence of nephritis. He quotes a case he recorded in 1890.<sup>28</sup> It was that of a girl who had nephrectomy done for bleeding from the kidney, and seventeen years after there had been no return of the bleeding. He believes that there is such a thing as essential renal haemorrhage from a kidney which may show no naked-eye or histological changes, and which appears to be a perfectly healthy kidney, and he gives references to seven cases in point. He dismisses the argument that because an excised piece of the kidney is healthy microscopically it does not follow that the whole kidney is healthy, and he does not think the bleeding ought to be called neuropathic or angioneurotic, but that these cases of essential renal haematuria should really be regarded as renal haemophilia.

Having carefully read the whole of the literature to which I can obtain access in London I am driven to the opinion that Senator is correct in his belief

<sup>23</sup> Hildebrandt, 'Essentielle Haematurie,' *Berl. klin. Woch.*, 1908.

<sup>24</sup> L. Spitzer, 'Zwei seltene Beobachtungen von Nierenblutung,' *Allgem. Wiener med. Zeitung*, 1909.

<sup>25</sup> T. Bleek, 'Ueber renale Massenblutungen. Ein Beitrag zur Frage der einseitigen Nephritis,' *Beiträge zur klin. Chir.*, 1909, lxi.

<sup>26</sup> Ritter, *Deutsch. med. Woch.*, 1910, 780.

<sup>27</sup> H. Senator, 'Ueber essentielle Nierenblutungen und renale Hämophilie,' *Berl. klin. Woch.*, 1910, 205.

<sup>28</sup> H. Senator, 'Ueber renale Hämophilie,' *Berl. klin. Woch.*, 1890.

that bleeding may take place from the kidney without there being any evidence to the naked eye or microscope that the organ is diseased. This is the condition for which the name 'essential renal haematuria' should be reserved. It is true that some cases in which bleeding has occurred from the kidney in the course of nephritis have been described as examples of essential haematuria, and probably some cases of bleeding from varicose veins of a renal papilla have also been recorded under this name, but even when with the most stringent criticism all these are allowed for, cases of genuine essential renal haematuria remain.

During the last twelve years there have been in Guy's Hospital five cases in which the kidney has been explored on account of bleeding from it, and the organ has appeared to be healthy. Mr. K. H. Digby, the Surgical Registrar, has kindly given me the patients' addresses and I have written to each, and I am indebted to my colleagues on the surgical side for permission to refer to them. They are as follow:—

*Case I.* Rose E., aged 36 years, admitted under Mr. Symonds in 1907. The patient had had pain in the right renal region together with, at times, haematuria since March, 1904. On February 8, 1907, a right-sided nephrorraphy was performed. The patient was re-admitted on November 22, 1908. The haematuria had continued and was so profuse as to endanger her life. The right kidney appeared to manual examination to be enlarged. The X-rays did not reveal a calculus. No tubercle bacilli could be found in the centrifugalized deposit from the urine. The bladder when examined by the cystoscope appeared normal. On January 8, 1909, the right kidney was explored and incised, its pelvis was opened and the ureter was catheterized. Nothing abnormal was found; the haematuria continued to be severe. On January 20, 1909, the right kidney was excised. No abnormality could be seen except a small infarct in the neighbourhood of a stitch. Microscopical sections showed the kidney to be healthy except for a minute patch of inflammation in connexion with the infarct. In reply to a letter from me the patient wrote to me on April 6, 1911. She says: 'For the last ten months I have been very well; I have not been like it for years. Ten months ago I weighed 6 st. 8 lb. 10 oz., now I weigh 7 st. 8 lb. 0 oz. I am as I never expected to be again. A year ago I felt ill and passed a lot of blood in the urine.'

*Case II.* Robert B., aet. 34, admitted under Mr. Fagge, November 4, 1907. Passed blood in the urine fourteen months previously. Right-sided pain and haematuria whenever during the last two months the patient had taken exercise. On November 8, 1907, the right kidney was explored and incised, the ureter also was incised; no abnormality could be found except some inflammation around and outside the upper part of the right kidney. I wrote to the patient and he replied on March 26, 1911. He writes that since he left the hospital he has had none of the old pain, and no blood in the urine. This used to come on after exercise, but now even heavy work does not lead to any bleeding. He says he is at present strong and healthy and has just passed a medical examination previous to going to Australia. He thinks he passes water a little more frequently than formerly.

*Case III.* Edith B., aged 38, admitted under Sir Alfred Fripp, July 20, 1908, giving a history of pain in the right loin for two years, together with one attack of haematuria. The right kidney was exposed but not incised, no calculus was felt, nephrorraphy was performed. I wrote to her, and she replied April 5, 1911, saying that since she left the hospital she had not passed any blood in the urine, but she had had one attack of pain in the side. Ever since she left the hospital she had been wonderfully well.

*Case IV.* Mary M., aged 25, was admitted under Mr. Arbuthnot Lane March 26, 1909, on account of right lumbar pain and haematuria. Blood had been noticed in the urine the previous June and November. The X-rays did not show any stone. March 30, 1909, the right kidney and ureter was thoroughly explored and appeared to be healthy in all respects. After the operation the haematuria ceased. I wrote to the patient, and she came to see me on April 13, 1911. Soon after she left the hospital she married. She has had no children, nor has she become pregnant. She has had no illness since she left the hospital, does her work well, sometimes rides her bicycle fifty miles in a day. Considers herself perfectly healthy, occasionally has a little lumbago. Menstruation quite regular. Her weight is constant. I found the lungs, heart, and arteries perfectly healthy, and the patient appeared to be in every respect in excellent health. Her heart was not hypertrophied; her blood pressure was 128 mm. of mercury. The kidneys could not be felt, they were not painful. There had been no blood in the urine since she left the hospital. The urine I examined was of good colour, specific gravity 1.026. It contained no blood, albumin, sugar, or casts. The urea was 3.2 per cent. The quantity passed was normal. Her eyes were normal.

*Case V.* William H. B., aged 36, admitted under Mr. Arbuthnot Lane, May 10, 1898, with nine months' history of abdominal pain, accompanied by about a dozen attacks of haematuria. Between the attacks of bleeding the urine contained no albumin. The X-ray examination and sounding the bladder were both negative. The pain was always in the region of the right kidney, which was palpable and somewhat tender. This kidney and its ureter were thoroughly explored, and nothing abnormal was found. I heard from the patient in May, 1911: he says he is quite well, but at different times he has passed much blood in his urine, but none for the last eighteen months.

It will be noted that in No. 1 the excised kidney was healthy, but the patient has, since the excision, passed some blood in the urine. This suggests that in rare cases of essential renal haematuria the blood may come from either kidney; that the blood came originally from the excised kidney is shown by the cessation for a long while of the profuse haematuria which followed excision; it is interesting, too, to notice how the health improved after the nephrectomy. The kidney in Case II was not examined microscopically, but as for three and a half years after nephrotomy the patient had seen no blood in the urine he cannot have had a varicose condition of the veins of the papillae, and as he had been in excellent health and had passed a medical examination just before I wrote to him, I think we may conclude he had not got nephritis. Case III was in such excellent health three years after the operation that she can hardly have had nephritis, and as the haemorrhage had not recurred during that time, we may conclude that she had not varicose papillary veins. The kidney in Case IV was thoroughly explored at the operation and appeared healthy. I examined the patient more than two years after. She had not passed any more blood, the urine and vascular systems were perfectly normal; she was able to bicycle fifty miles a day; she appeared to me, after I had examined her very thoroughly, to be in excellent health, so I think we may conclude that her previous haematuria was not due to nephritis. Case V was perfectly well thirteen years after operation, but during these years he had had attacks of haematuria, although no varicose veins of the papillae were seen at the operation.



It might be urged that these patients had had nephritis but they had recovered; but in none was there before the operation any single symptom save the hæmorrhage and sometimes pain, the kidney appeared healthy at operation, and all the patients were well when seen years after the operation, and it must be remembered that they were at an age at which ordinary chronic nephritis does badly. We must, it seems to me, conclude that they were examples of essential renal hæmaturia.

This condition occurs in both men and women, but more often in men; the patients are nearly always between the ages of 20 and 40 years, and usually under 30. It is very rarely fatal, and although no doubt the hæmorrhage sometimes ceases spontaneously, its cessation so often follows after nephrotomy that it is difficult to resist the conclusion that this operation is often beneficial, but in Cases I and V hæmaturia has returned since operation, nevertheless each patient now feels well. Nephrectomy should not be undertaken unless the patient's life is in danger from loss of blood. Why a nephrotomy does good we cannot say, for we do not know the cause of the hæmorrhage, but there must be a solution of the continuity of some of the renal vessels, or else the red cells could not pass out. There seems no support for Senator's suggestion that the patients are sufferers from hæmophilia; they do not bleed from elsewhere, the hæmaturia does not follow injury, nor does it occur in families. There is no reason for calling it angioneurotic or neuropathic, and doing so does not help us to understand it. Vicarious menstruation does not aid us, for most of the patients are men. When an explanation is found, we may perhaps be helped to it by remembering that the apparently healthy kidney will sometimes allow albumin to pass into the urine, as in the albuminuria of adolescence and that which follows severe exercise; indeed, sometimes blood may appear in the urine after great exertion, and also the apparently healthy kidney will allow of the passage into the urine of large quantities of Bence Jones protein. Essential renal hæmaturia appears to have its closest parallel in epistaxis; we are reminded, too, of oozing of blood from the gastric mucous membrane, or gastrostaxis as it is sometimes called, although in this condition there are a number of quite minute ulcers; indeed, were there not, the blood could not get into the interior of the stomach. Whether these ulcers are formed by blood bursting through the mucous membrane, or whether the bleeding is due to a number of minute ulcers opening vessels, is not yet decided. The most feasible suggestion appears to be that in some people a poison is formed somewhere at intervals, and this reaching the kidney by the blood damages the cells of the minute vessels so as to let blood through. That substances circulating in the blood may cause hæmorrhage, that is to say, damage the lining of minute blood-vessels, so that they give way and blood passes out, is shown by several facts. For example, bile circulating in the blood causes hæmorrhage, as is seen in the very severe purpura that may occur in jaundice. Patients with splenic anaemia suffer from hæmatemesis early in the disease, before the liver is affected, and the most plausible suggestion is that this is due to some poison circulating in the blood, and that this is formed presumably in the spleen. Again,

those who have cirrhosis of the liver are liable to purpura, even if they are not jaundiced. Perhaps the gastro-intestinal ecchymosis so frequently seen in cases of septicaemia has the same explanation, although here the suggestion of minute ulcers is possible. Then, too, there must be something which damages the minute vessels in purpura haemorrhagica and Henoch's purpura, and also in the haemorrhagic varieties of the exanthemata. Whether or not there is a deficiency in the coagulability of the blood does not bear upon the question of why the blood leaves the vessels, as mere diminution of coagulability will not give it the power to do so; for the red cells to come out of the vessels there must be a damage to the vessel walls, and if it were urged that infinitely slight traumatic damage to the renal vessels led to the bleeding, which was severe because of delayed coagulation, it might at once be answered that if this were the case the patients would bleed from elsewhere, like a haemophilic, but they do not. It is no doubt strange that in essential renal haematuria the bleeding takes place only from the kidney, but that these substances, which circulating in the blood damage vessel walls, may act only on certain vessels is shown by the fact that haematemesis, and not a general bleeding, is common in splenic anaemia, and further the internal secretion of the ovary which leads to the menstrual flow acts only on the uterus. It is perhaps conceivable that the trouble is due to the passage of bacteria from the blood through the kidney into the urine; this must be settled by future investigation, but it must be remembered that in two of Kotzenberg's cases the urine was examined bacteriologically without finding any micro-organisms.

The five original cases here published have been followed for much longer periods than almost all other published cases, and from them we learn that the outlook is good and that the disease does no harm apart from the loss of blood.

#### REFERENCES.

CHIEF REFERENCES SINCE THOSE GIVEN BY H. L. KRETSCHMER, *Zeitschrift für Urologie*, 1907, i. 490.

- Bleek, T., 'Ueber renale Massenblutungen. Ein Beitrag zur Frage der einseitigen Nephritis,' *Beiträge zur klin. Chirurgie*, Tübing., 1909, lxi. 398.
- Bunts, 'Essential Haemorrhage of the Kidney,' *Cleveland Med. Journ.*, 1908, vii. 317.
- Christian, H. M., 'Haematuria of Renal Origin,' *New York Med. Journ.*, 1907, lxxxvi. 778.
- Elliott, A. R., 'Obscure Renal Haematuria,' *International Clinics*, Philadelphia, 1906, 16th ser., iv. 122.
- Golling, J., Inaugural Dissertation abstracted in *Zeitschr. f. Urologie*, 1909, 104.
- Heymann, A., 'Einseitige renale Hämaturie,' *Deutsch. med. Woch.*, 1907, xxxiii. 325.
- Hildebrandt, 'Essentielle Haematurie,' *Berl. klin. Woch.*, 1908, xlv. 470.
- Karaffa-Korbutt, 'On so-called Essential Haematuria,' *Folia Urolog.*, Leipzig, 1907, i. 323.
- Abstract, *Zeitschr. f. Urologie*, 1908, 376.
- Kennedy, J. P., 'A Case of Obscure and Symptomless Renal Haematuria,' *Dominion Medical Monthly*, Toronto, 1907, xxviii. 193.
- Kotzenberg, W., 'Ueber Nierenblutungen,' *Med. Klinik*, Berl., 1907, iii. 1515.
- Kotzenberg, W., 'Ueber Nierenblutungen,' *Zeitschr. f. Urologie*, 1908, ii. 125.
- Lane, J. E., 'A Case of Profuse Renal Haematuria,' *New York Med. Journ.*, 1907, lxxxvi. 835.

- Marocchi, A., 'Ematurie renali,' *La clinica chirurgica*, No. 2, p. 317. Abstract, *Zeitschr. f. Urologie*, 1910, iv. 543.
- Milkó, W., 'Ueber die sogenannten essentiellen Nierenblutungen,' *Ungar. med. Presse*, Budapest, 1907, xii. 1-4.
- Pincus, *Deutsch. med. Woch.*, 1908, xxxiv. 1980.
- Pousson, A., 'Néphrites chroniques hématuriques,' *Folia Urologica*, Leipz., 1907, i. 295. Abstract, *Zeitschr. f. Urologie*, Leipz., 1908, ii. 375.
- Ritter, 'Essentielle Nierenblutung,' *Deutsch. med. Woch.*, 1910, xxxvi. 780.
- Schüller, 'A Clinical Lecture on Essential Nephritic Haemorrhage,' *Med. Press and Circular*, 1906, lxxxi. 62.
- Senator, H., 'Ueber essentielle Nierenblutungen und renale Hämophilie,' *Berl. klin. Woch.*, 1910, xlvii. 205.
- Spitzer, L., 'Zwei seltene Beobachtungen von Nierenblutung,' *Allgem. Wiener med. Zeitung*, 1909, lix. 1.
- Steinthal, 'Zur Kenntnis der essentiellen Nierenblutungen,' *Beiträge zur klin. Chirurg.*, 1907, liii. 772.
- Treplin, *Deutsch. med. Woch.*, 1909, xxxv. 103.

#### REFERENCES TO PAPERS PREVIOUS TO KRETSCHMER'S BUT NOT INCLUDED IN HIS LIST.

- Albarran, *Presse médicale*, Paris, 1904, ii. 657.
- Edwards, S., 'Nephrotomy and Nephrorrhaphy for Symptomless Haematuria,' *Med. Press and Circular*, 1903, lxxvii. 723.
- Eshner, A. A., 'Unilateral Renal Haematuria,' *Amer. Journ. Med. Sciences*, 1903, N. S. cxxv. 636.
- Guisy, B., 'Trois cas d'hématurie hystérique,' *Prog. méd.*, Paris, 1902-3, xxii. 177.
- Illyés, 'A Case of Essential Renal Haemorrhage,' *Orvosi Hetil*, Budapest, 1905, xlix. 889.
- Jaboulay, 'Hématurie rénale datant de quatre ans; capsulectomie et néphrolyse: guérison,' *Lyon méd.*, 1905, civ. 989.
- Lancereaux, 'Hémorragies névropathiques des organes génito-urinaires,' XIII<sup>e</sup> Cong. internat. de Méd., Section de Pathol. gén. et Pathol. expér., 1900, Paris, 1901, *Compt. rend.*, 125-30.
- Malherbe et Legueu, *L'Assoc. française d'Urologie*, 1899.
- Morris, H., *Surgical Diseases of the Kidney and Ureter*, London, 1901, i. 591.
- Nothnagel, *Encyclopaedia of Practical Medicine*, English Edition, Vol. on Diseases of the Kidney, &c., Philadelphia and London, 1905, 54.
- Rayer, *Traité des Maladies des Reins*, Paris, 1841.
- Rosving, T., 'On Obscure Haemorrhage from a Single Kidney and its Cure by Nephrotomy,' *Brit. Med. Journ.*, 1898, ii. 1547.
- Sehenck, B. R., 'Renal Haematuria of Unexplained Origin; Cessation after Nephrotomy,' *Med. News*, New York, 1904, lxxxv. 1206.

## CRITICAL REVIEW

### THE USE OF TUBERCULIN IN SO-CALLED 'TUBERCULOUS' GLANDS

By GEORGE E. WAUGH

THE views of many writers as to the value of tuberculin in the treatment of tuberculosis of glands are still varied and conflicting. It is not surprising, therefore, that some surgeons of authority and experience ignore it entirely as a therapeutic agent of value for this condition. Thus Andrews, of Chicago (1), in his article on tuberculous glands in the neck in Keen's *Surgery*, 1909, makes no reference to it amongst other conservative measures that he advises. Holt (8), in writing of the same condition in his textbook on 'The Diseases of Children', 1910, ignores its existence. Klebs (9) writes that 'the most satisfactory and lasting results are obtained by extirpation, unless the vaccine therapy of Wright proves to be of greater service than can at present be predicted'. Bosanquet and Eyre (5), quoting Adrian, report that 'new tuberculin has no effect on tubercular diseases of bones or glands'. Western (12), in the treatment of 40 cases, 'could not report unqualified success as was reported by Sir A. E. Wright.' Bennett (4) regards the good effects ascribed to tuberculin as 'being possibly due to the fresh air and good food, especially in hospital patients'. Allen (2) summarizes the value of vaccine inoculation as follows:—'Out of 8 cases there is an expectation of marked improvement in 5, slight improvement in 2, and complete failure in 1 or 2.' Carmalt-Jones (6), out of 79 cases treated by inoculation, reports that '27 were cured, 22 much better, 18 better, 8 unaltered, 4 worse'. Lastly, Nathan Raw (11) regards 'glands in the neck as the most favourable lesions for treatment with human tuberculin'. The views of Wright and his school are too well known to need more than a passing reference. A good summary from the surgical point of view with appropriate reference to the proportional value of tuberculin is made by Clayton-Greene (7).

To give or to withhold tuberculin in the treatment of these cases, therefore, could easily be justified by reference to authorities. The discrepancies of their views can be comprehended by reference to the complexities of the problem. The value of tuberculin can clearly only be appraised by the effect of its administration in tuberculous cases. No *proof* is given by the writers quoted above that the enlargement of the glands in the cases treated was due to the

action of the tubercle bacillus. To expect success this should have been the sole cause of the enlargement. The assumption that the persistence of a chronic enlargement of a gland is due to the tubercle bacillus is valueless. Investigation of the glands *after removal* in cases clinically identical often fails to show any evidence of a tuberculous lesion, whilst the presence of other infective agents is no infrequent occurrence. *Treponema*, *streptothrix*, *Staphylococcus albus*, and the pneumococcus, in addition to the tubercle bacillus, are common causes of chronic glandular enlargement. Allen (2) states that only 60 per cent. of chronically enlarged glands are tuberculous, and he finds that 'out of 58 cases, 33 contained bovine, 24 human, and 1 both tubercle bacilli'. Clinical evidence that a pulmonary lesion is tuberculous has long been disregarded, but it is still a cherished tradition that clinical evidence of chronic enlargement of glands in the neck is proof that that enlargement is due to the action of the tubercle bacillus. Clinical signs are merely evidence of the nature and degree of the tissue change in any organ and cannot be accepted as a proof of the particular cause of that tissue change. (In spite of that obvious truth one is frequently appealed to to decide by palpation of enlarged glands whether they are 'tuberculous' or not—as if some special merit resided in one's fingers that was not present in the fingers of the questioner, and made an excellent substitute for precise and scientific laboratory investigation!) Holt (8) writes in 1910: 'The diagnostic features of tubercular glands are the age of the patient, the site of the primary swelling, the indolent course and the disposition to show caseation, softening, and abscess.' Comment is unnecessary, but it is clear that the tradition will die hard.

The reactions following skin inoculation by von Pirquet's method have a limited value. A positive result may be accepted as evidence that the patient has a tuberculous lesion somewhere. It is not proof that that lesion is resident in the glands under investigation. A negative reaction may occur in a patient known to be suffering from tuberculosis. Two of the cases of abdominal tuberculosis included in this list, which proved to be tuberculous after the performance of laparotomies, gave repeated negative reactions to the von Pirquet test.

To judge, therefore, of the value of tuberculin injections in cases where the only evidence that the affected glands are tuberculous is of a clinical nature, is likely to lead to a conflict of opinion, and possibly explains many of the discrepancies.

Secondly, the important rôle played by constant re-infection in the perpetuation of the chronic enlargement of glands seems to be improperly appraised. Nearly all the writers alluded to lay great emphasis upon curative measures directed towards the prevention of this, such as the care of the teeth, scalp, and ears, and the removal of tonsils and adenoids, but they make no attempt to differentiate between this treatment and the injection of some form of tuberculin, in determining the main factor in the achievement of a successful result. There is a distinct bias towards the most novel form of treatment, i.e. treatment by

injection. Nor is there sufficient proof that their attempts to prevent re-infection were successful in cases where the adoption of both measures had failed to ward off surgical interference with the glands. The use of the guillotine for lopping off a portion of a diseased tonsil is an entirely unsatisfactory method of preventing re-infection via that route. That the tubercle bacillus itself may enter from the tonsil is shown by Matthews, 1910 (10), who isolated it from the tonsils in 5 out of 8 cases of chronic enlargement of glands in the neck.

Thirdly, areas of dead tissue containing infective agents may be present in the centre of enlarged glands without being detectable by clinical means. Examination of glands after removal shows how repeatedly this condition is present. Tuberculin injections can clearly exert no more influence upon these areas than can mercury and iodide of potassium upon the central necrotic area that may be present in an unbroken gumma. The value of tuberculin may, therefore, be unduly discounted, since this condition, clinically undetectable, may be present from the time of the beginning of the course of injections.

Lastly, all varieties and doses of tuberculin find alike a host of advocates and censors (Bandelier and Roepke (3)). The reasons for the attitude assumed are not clearly stated as a rule. Nevertheless, it is of sufficient significance to permit of the assumption that an ideal combination of fluid and dosage has not yet been discovered.

With a full appreciation of the fallacies of the evidence upon which any conclusions must be based, the writer has attempted to form some estimate of the value of one form of tuberculin and one method of dosage from an investigation of 191 cases under his care during the last few years at the Children's Hospital, Great Ormond Street. Seven were cases of abdominal tuberculosis with enlarged mesenteric glands, one was a case of enlarged inguinal and iliac glands without a detectable primary focus of infection, two were cases of enlarged glands in the neck, with multiple tuberculous foci in the small bones of the hand and foot and with no other detectable foci of infection, whilst the remaining 181 cases had chronic enlargement of glands in the neck, with primary foci of infection that were obvious and required treatment to eliminate re-infection as a source of failure. The treatment of those 181 cases only differed in one particular: all of them had the source of re-infection stamped out, 51 had injections of tuberculin administered, 130 had not. There was no selection of cases. No cases had had tuberculin in the first 130, all cases had it subsequently as an additional element of treatment with a view, if possible, of testing the value claimed for it by many writers. In the treatment of primary foci of infection 60 per cent. of the cases passed through the dental department for the extraction or stopping of carious teeth. All of the 181 cases had their tonsils dissected out and from most of them adenoids were removed as well. More than half of these had previously had their tonsils guillotined and were still suffering from chronic glandular enlargement. The amount of septic tonsillar material subsequently removed by the operation of dissecting afforded ample reason for the persistence of the gland trouble.

No cases in which immediate surgical interference seemed advisable are included in this list of 181 cases, that is to say, cases in which sinus formation, softening, fluctuation, or adherence to the subcutaneous or deep structures of the neck had occurred before they began their attendance at the Children's Hospital, Great Ormond Street. Many cases ceased to attend during the course of treatment, and they also have been excluded from the list. No cases of acute inflammation are included, and cases which after further investigation proved to be syphilitic or lymphadenomatous are excluded.

The form of tuberculin used was Wright's bacillary emulsion. No smaller dose than  $\frac{1}{5000}$  mg. was ever employed, and the largest dose was  $\frac{1}{2}$  mg. The injections as far as possible were made at intervals of one week in this order:  $\frac{1}{5000}$ ,  $\frac{1}{4000}$ ,  $\frac{1}{3000}$ ,  $\frac{1}{2000}$ ,  $\frac{1}{1000}$ ,  $\frac{1}{800}$ ,  $\frac{1}{600}$ ,  $\frac{1}{500}$ ,  $\frac{1}{400}$ ,  $\frac{1}{300}$ ,  $\frac{1}{200}$ ,  $\frac{1}{100}$  mg. The last dose was frequently repeated several times, while five cases passed on by degrees to  $\frac{1}{10}$  and  $\frac{1}{2}$  mg. No estimation of the opsonic index was made, and apparently no 'negative phase' was ever encountered. One patient received  $\frac{1}{100}$  mg. every week for a period of nearly five months. In no case did rapid enlargement of the glands occur, no metastatic foci made their appearance, and no rapid formation of abscesses occurred. In only a small proportion of the cases was any malaise experienced soon after the injections. A slight headache was the most frequent phenomenon, which coincided as a rule with the administration of  $\frac{1}{1000}$  or  $\frac{1}{300}$  mg. That particular dose was repeated before passing on to the next higher one. The average number of injections each patient received was 16 to 20, although some only required 6 to 8 injections, whilst a few had as many as 50 or 60.

Of the 130 cases treated without tuberculin, 16, or 12.3 per cent., had the radical operation for the removal of the glands subsequently performed. Thirteen, or 10 per cent., had small abscesses subsequently excised and closed without drainage. The remainder recovered without further specific treatment after a period of four to six months from the date of the operation on the primary focus of infection.

Of the fifty-one cases of glands in the neck treated *in addition* with the injections of tuberculin, ten, or 19.6 per cent., had the glands subsequently removed by a radical operation; six of these were proved to be tuberculous. Nine, or 15 per cent., had abscesses subsequently opened and stitched. The remainder recovered after a period of treatment of about seven months' duration from the date of the operation on the primary focus of infection.

The seven cases of abdominal tuberculosis were all treated with tuberculin. On five of them I performed laparotomy; all seven cases recovered.

The two cases of glands in the neck with no primary foci of infection but with bone lesions recovered without any operation. They both had tuberculin.

The case with enlarged glands in the groin had the inguinal and femoral groups removed; the iliac group disappeared after a course of tuberculin injections. Tubercle bacilli were not found in the glands that had been removed.

TABLE.—*Glands in Neck and Groin.*

No. of Cases.	Primary focus.	Tuberculin.	Radical gland operation.	Local abscess formation.	Cures.
130	Tonsils dissected out from all	Nil	16, i.e. 12.3 %	13, i.e. 10 %	101
51	Tonsils dissected out from all	All	10, i.e. 19.6 %	9, i.e. 15 %	32
3	No primary foci of infection	All	—	—	3

*Abdominal Tuberculosis.*

No. of Cases.	Primary focus.	Tuberculin.	Operation.	Local abscess formation.	Cures.
7	—	All	Laparotomy on 5.	—	7

*Conclusions.*

1. That any estimate of the value of injections of tuberculin in the treatment of enlarged glands must be invalidated by the fact that no *proof* that the glands were tuberculous can be offered until the glands have been subjected to operation.

2. That the most important factor in the treatment of chronic glandular enlargement with a view to the avoidance of extensive operative interference is the complete elimination of all primary foci of infection. The use of the guillotine to the tonsils is one of the most serious causes of failure in the treatment of enlarged glands.

3. That the use of Wright's bacillary emulsion in the doses already described as an additional element of treatment has not yet proved to be of any value.

4. That, judging by the absence of marked constitutional or local disturbance following administration by this method, the fluid is harmless, and may be accorded a more extensive trial.

5. That in cases of enlarged glands which were removed and were then proved to be tuberculous, a thickening of the scar of operation frequently occurred. This thickening as a rule disappeared under a course of injections of tuberculin.

## REFERENCES.

1. Andrews, *Kee's Surgery*, Lond., 1909, iii.
2. Allen, *Vaccine Therapy, its Theory and Practice*, Lond., 1910.
3. Bandelier and Rocpke, *Tuberculin in Diagnosis and Treatment*, transl. by Morland, Lond., 1909.
4. Bennett, Sir W., *Practitioner*, Lond., 1910, lxxxiv. 741.
5. Bosanquet and Eyre, *Scrums, Vaccines, and Toxines*, Lond., 1909.
6. Carmalt-Jones, *Brit. Med. Journ.*, 1909, ii. 531.
7. Clayton-Greene, *Index of Treatment*, Bristol, 1910.
8. Holt, *Diseases of Children*, Lond., 1910.
9. Klebs, *Tuberculosis* (by American authors), Lond., 1910.
10. Mathews, *Annals of Surgery*, Philad., 1910.
11. Raw, N., *Lancet*, Lond., 1910, i. 844.
12. Western, G. T., *Lancet*, Lond., 1907, ii. 1375.